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American Heart Journal

VOL. 49 MAY, 1955 No. 5

Original Communications

BALLISTOCARDIOGRAPHIC STUDY OF BODY ACCELERATION DURING THE ACUTE AND CONVALESCENT STAGES OF RHEUMATIC FEVER

S. R. ARBEIT, M.D., M. A. DOLAN, M.D., AND GENE H. STOLLERMAN, M.D.

IRVINGTON, N. Y.

THE application of ballistocardiography to the clinical study of acute and chronic rheumatic fever in children has been hampered by the limitations of instruments which measure only the displacement or velocity of body motion. The applied forces of cardiac action are not always accurately reflected by the displacement or the velocity of body motion.[1,2] This is particularly true in the presence of tachycardia.[3] Because sinus tachycardia is encountered so often in children, studies of rheumatic carditis employing the conventional displacement and velocity ballistocardiogram have met with difficulty.[4]

The recent development of the acceleration ballistocardiogram[1,2] has made possible the accurate recording of body motion in response to the application of high-frequency forces. Consistent and reproducible ballistocardiographic complexes are recorded by the measurement of body acceleration even in the presence of marked tachycardia.

In preliminary studies reported here employing the Arbeit and Lindner instrument,[1] significant variation of the acceleration ballistocardiogram (BCG) was rarely observed in normal children.* An empirical clinical study was therefore undertaken to determine whether deviation from the normal acceleration ballistocardiogram could be correlated with various stages of rheumatic fever.

This study comprises an analysis of 1,400 BCG's obtained from 320 different children. The data presented indicate that significant BCG abnormalities occur frequently during the acute stage of the disease and tend to disappear during convalescence.

From Irvington House and the Department of Medicine, New York University College of Medicine, New York, N. Y.

Supported in part by a grant from the Masonic Foundation for Medical Research and Human Welfare, Irvington-on-Hudson, N. Y.

Received for publication Sept. 24, 1954.

*See classification, Table I.

MATERIAL AND METHODS

The instrument* employed in these studies has been described in detail elsewhere.[1] Ballistocardiograms of body acceleration, velocity, and displacement were recorded with a direct-writing two-channel electrocardiograph (Sanborn twin-viso cardiette). Lead II of the electrocardiogram was obtained simultaneously. All BCG's were taken with children at rest supine on a firm wooden table. BCG's were obtained routinely according to the following schedules: on all patients at the time of admission; every two weeks in patients with clinical rheumatic activity; monthly in patients with abnormal BCG's who had no clinical evidence of rheumatic activity; every three months in patients in whom the BCG was normal (on at least two consecutive records) and in whom clinical rheumatic activity was not evident; on all patients at time of discharge from Irvington House.

BCG's were read independently by at least two of the authors without knowledge of the patient's clinical status. In addition fifty-seven tracings were reviewed and classified by an independent observer† who did not participate in this study. The records chosen for restudy were those taken from the convalescent group who had no evidence by history or clinical course of any previous carditis. There was 100 per cent agreement on the Grade 1 and the Grade 2 tracings. In the transition zone between Grade 1 and Grade 2 there was as much as 13 per cent disagreement between any two observers. These differences of opinion were primarily concerned with determining precisely when the patient's record changed from abnormal to normal. In only one case (F.P.) would there have been an effect on the validity of our gross statistical study, and this would have been in the direction of adding another abnormal to the early convalescent group.

The group of children studied was composed of equal numbers of boys and girls ranging in age from 6 to 15 years who were hospitalized at Irvington House during various stages of attacks of acute or chronic rheumatic fever. They were observed until all evidence of the disease had subsided and for approximately six months thereafter during convalescence. At weekly intervals during the acute stage of the disease, and monthly during convalesence, blood samples were obtained for serologic tests, erythrocyte sedimentation rate, C-reactive protein determinations, and white blood cell counts. Electrocardiograms and teleroentgenograms were obtained at similar intervals. Most patients were treated with either cortisone, ACTH, or acetylsalicylic acid. The dosage of these was varied freely in most instances according to the clinical response of the patient. In general, treatment was initiated with daily doses of either 300 mg. of cortisone administered orally or intramuscularly, 120 mg. of ACTH, or 1 grain of acetylsalicylic acid per pound of body weight. The dose thereafter was gradually reduced and treatment was continued for a period of six to twelve weeks.

---

*The instrument used in this study was provided by Industrial Development Laboratories, Jersey City, N. J.

†Dr. A. Ancowitz, Section Chief, Internal Medicine, V. A. Hospital, Bronx, New York.

All patients included in the study met the criteria of Jones[5] for the diagnosis of rheumatic fever at some time during the course of their disease. Patients were grouped as follows.

Group 1: This group consisted of those patients observed during a period of frank rheumatic activity, indicated by the simultaneous presence of at least one major manifestation (carditis, polyarthritis, subcutaneous nodules, or chorea) and two minor manifestations (fever, elevated erythrocyte sedimentation rate, presence of C-reactive protein, erythema marginatum, prolongation of the P-R interval, or other abnormal electrocardiographic changes) or by the presence of two major manifestations. In addition, patients with congestive heart failure were included in this category with or without the presence of any other rheumatic manifestations. Twenty-three patients were included in this group.

Group 2: This group consisted of those patients observed with definite low-grade rheumatic activity as evidenced by the simultaneous presence, following a frank rheumatic attack, of at least two of the following four minor manifestations: fever (at least 100.3° F. rectally), elevation of the erythrocyte sedimentation rate (ESR) to 15 mm. per hour or greater, positive test for C-reactive protein (CRP), prolongation of the P-R interval to 0.04 sec. beyond the values listed for various ages and cardiac rates in the tables of Ashman and Hull.[6] Ten patients were included in this group.

Group 3: This group was composed of fourteen patients recently recovered from a frank attack of rheumatic fever in whom a single isolated manifestation of possible rheumatic activity persisted such as elevation of ESR, persistence of CRP or prolongation of P-R interval, and in whom complete subsidence of the active process was doubtful.

Group 4: This group consisted of patients with so-called "pure" chorea as an isolated manifestation unassociated with any of the minor manifestations listed previously. Thirteen patients were included in this group.

Group 5: Convalescent patients in this category had recovered from acute rheumatic fever and were considered convalescents when all clinical and laboratory evidence of rheumatic activity had disappeared. Ninety patients were included in this group.

Classification of Ballistocardiograms.—Ballistocardiograms were classified as either "normal" or "abnormal". The "normal" record followed in general the criteria of Brown and associates[7] for a classification of Grade 0 or I. The "abnormal" were further subdivided as illustrated in Table I. The classification was based on the acceleration curve. Records were not considered abnormal on the basis of changes in the d or v curve alone, since these were frequently associated with normal acceleration curves. Conversely, an abnormal acceleration tracing was often seen with a normal or near normal displacement or velocity curve. Our analysis of the physical system of the BCG has led us to interpret these as meaning that though the slowly applied forces had not changed from the normal, the more rapidly applied forces had been altered by the underlying pathology. These traces were therefore classified as abnormal.

TABLE I. CLASSIFICATION OF BCG (IRVINGTON HOUSE STUDY) BASED ON THE ACCELERATION CURVE

NORMAL
*Grade 1 corresponding to Brown and associates' "I" and "0"**
1. Regularity, repetitiveness, and definitiveness preserved (individual peaks of IJK easily defined).
2. Amplitude varies less than 50 per cent of IJ in expiration.
3. Notches and slurs in individual waves may be present.
"ABNORMAL"
Grade 2 corresponding to Brown and associates' II and III
1. Regularity lost (variation in form from complex to complex), or some complexes are still identifiable.
2. Amplitude and/or repetitiveness varies more than 50 per cent with respiration.
Grade 3 corresponding to Brown and associates' IV
1. Chaotic pattern. Loss of identifiable complexes.

These criteria are not sharp, clear cut, and susceptible to quantitative definition. However, as in other clinical interpretations, there is a borderline transition zone between grades that at present is qualitative.

*Brown, H. R., et al.: Clinical Ballistocardiography, New York, 1952, The Macmillan Co.

Minor deviations of form such as notching or slurring of individual waves of the complex in the acceleration record were not considered sufficient to classify the BCG as "abnormal" as long as they were repeated in successive complexes, since these were observed to occur frequently in the normal control group. Similarly, notches and slurs which were seen in the records of patients with rheumatic valvular deformity were not read as "abnormal" for the purposes of this study. The designation of "abnormal" was applied only to BCG's classified as at least Grade 2. Variations of this degree were rarely observed in the control series of normal children.

RESULTS

Control Group.—One hundred children, ages 5 to 15, who appeared at a general dispensary* for minor illnesses or routine physical examination, were studied. Forty children in this group were entirely asymptomatic and had no significant abnormal physical findings. Sixty reported to the dispensary for a variety of minor upper respiratory infections and childhood diseases. All patients were studied medically, and all with heart disease or suspicion of rheumatic fever were excluded. In all patients, displacement, velocity, and acceleration BCG's were obtained. The acceleration BCG was classified as Grade 0 in 20 per cent, and as Grade 1 in 80 per cent of this group. No patient in this control group had an acceleration BCG which could be classified as a Grade 2. A second control group† consisted of fifty healthy school children, ages 12 to 14,

*Fort Hamilton Station Hospital, Lt. Col. Milton Hollander, M.C., C.O.

†The cooperation of the students and faculty of the Hastings Public School, Hastings-on-Hudson, New York, is gratefully acknowledged.

who had no history of recent illness or previous cardiovascular disease. The records were taken during a regular school day. Two of these patients had definitely abnormal *d*, *v*, and *a* tracings. Further medical studies were not performed in these two cases, repeat tracings were not taken, nor was follow-up study undertaken for social reasons.

In view of these findings the BCG was not designated as "abnormal" in patients subsequently studied at various stages of rheumatic fever unless the acceleration BCG was consistently at least Grade 2 regardless of the apparent abnormality of the displacement or velocity BCG.

Ballistocardiograms in Patients With Active Rheumatic Fever Before Antirheumatic Treatment.—Of the total number of patients admitted to Irvington House during the period of this study, sixty were found to have clinical evidence of rheumatic activity. BCG's were obtained in this group prior to the institution of or resumption of antirheumatic therapy. The correlation of ballistocardiographic abnormality with the severity of the rheumatic process was as follows.

Group 1.—Frank rheumatic activity: Of twenty-three patients in this group, fifteen had significantly abnormal acceleration BCG's. Of the twenty-three patients, fifteen had clinically evident carditis. Of these, twelve had abnormal BCG's. In the remaining three patients with normal BCG's the diagnosis of active carditis was made on the basis of a changing murmur alone. In the presence of frank congestive heart failure the acceleration BCG was always grossly abnormal. All patients with pericarditis had at least a Grade 2 acceleration BCG. Of eight patients who had frank rheumatic fever without clinical evidence of carditis three had abnormal acceleration BCG's (Table II).

TABLE II. BALLISTOCARDIOGRAM CORRELATION WITH DEGREE OF RHEUMATIC ACTIVITY IN A GROUP OF 60 PATIENTS NOT RECEIVING THERAPY

SEVERITY OF RHEUMATIC ACTIVITY	NO. OF PATIENTS	GRADE OF ABNORMALITY		PER CENT ABNORMAL BCG
		GRADE 2*	GRADE 3*	
Group I				
Frank activity				
A. With clinical carditis	15	3	9	80
B. No clinical carditis	8	3	0	37
Group II				
Low grade activity	10	3	1	40
Group III				
Questionable activity	14	3	0	21.3
Group IV				
Pure chorea	13	1	0	7.7
Control Group				
Well children	150	2	0	1.3

*Irvington House study classification.

Group 2.—Low grade rheumatic activity: Of ten patients who were classified in this category four had abnormal BCG's. Clinical carditis had been evident in the earlier stage of frank rheumatic activity in all four patients in whom the BCG was abnormal (Table II).

Group 3.—Questionable rheumatic activity: Of fourteen patients studied, three had abnormal acceleration BCG's. Prior evidence of clinical carditis was present in all three (Table II).

Group 4.—Chorea: The BCG's of thirteen patients with Sydenham's chorea as an isolated manifestation were studied. Only one patient in this group had an abnormal BCG. This child had had acute rheumatic carditis five months prior to onset of chorea but had no residual signs of rheumatic heart disease at the time the BCG was taken.

TABLE III. BCG DURING THERAPY

	NAME	TYPE OF RHD (1)	CHF (2)	TYPE THERAPY (3) (4)	GRADE BCG PRIOR TO THERAPY	GRADE OF BCG IN WEEKS AFTER THERAPY†
Chronic carditis	D.V.	EH, AI, MI, MS	+	ASA, CORT	3	3 3 3 3 3 3
	L.D.	EH, AI, AS, MI, (MS)	+	ASA, CORT	2	2 2 2 2 2 2
	B.T.	EH, MI, MS	+	ASA, CORT	3	3 3 3 3 3 3
	W.R.	EH, MI, MS	+	ASA	3	3 3 3 3 3 3
	K.P.	EH, MI, MS	+	CORT	3	3 3 2 3 2 -
Acute rheumatic fever with carditis	W.C.	EH, AI, MI, MS	+*	CORT	3	3 3 3 2 3 -
	F.K.	EH, AI, MI, (MS)	+	ASA, CORT	2	2 2 2 1 1 -
	J.D.	EH, AI, MI, MS	+*	CORT	3	1 1 2 1 1 -
	H.L.	EH, AI, MI, MS	+*	CORT	2	2 1 2 1 2 -
	H.C.	EH, MI, MS	0	CORT	-	1 1 2 1 2 -
	H.S.	EH, MI	0	CORT	-	1 2 2 - - -
	E.C.	EH, MI	0	ASA	-	2 2 2 1 1 -
	C.D.	EH, MI	0	ASA, CORT	-	1 1 1 1 1 -
	H.T.	EH, MI	0	ASA	1	1 1 1 1 1 -
	P.A.	EH, MS	0	ASA	1	1 1 1 - - -
Acute rheumatic fever with no carditis	J.W.	No RHD	0	ASA, CORT		3 1 1 1 1 -
	R.R.	No RHD	0	ASA		1 1 2 1 - -
	W.K.	No RHD	0	CORT		1 1 1 1 1 -
	T.I.	No RHD	0	ASA		2 2 - 2 - -
	T.D.	No RHD	0	CORT		2 2 1 2 - -

*Pericarditis
†Columns represent 2, 4, 6, 8, 10, and 12 weeks after therapy.
(1) RHD = Rheumatic Heart Disease
(2) CHF = Congestive Heart Failure
(3) ASA = Aspirin
(4) CORT = Cortisone

Ballistocardiogram in Patients Receiving Antirheumatic Therapy (Table III).—Those patients with severe, protracted rheumatic carditis who showed little improvement in cardiac status during prolonged therapy with either cortisone or salicylates showed persistence of BCG abnormality.

Patients with acute carditis who improved clinically during therapy usually showed reversion of the BCG toward normal when abnormalities were present initially. This was particularly evident when patients with congestive heart failure regained cardiac compensation during treatment (Table III). In general, the BCG appeared to reflect the cardiac status of the patient rather than the

symptomatic response to the anti-inflammatory effects of therapy. The BCG's of patients receiving cortisone did not differ noticeably from those of patients with comparable cardiac involvement who received salicylates.

Patients who had no clinical evidence of carditis when treatment was instituted did not have marked BCG abnormalities (none were Grade 3). Further, clinical response in this group did not correlate closely with the BCG. Several patients whose joint symptoms responded promptly to treatment retained the BCG abnormality for many weeks thereafter (Table III). Subsequent reversion of BCG to normal in this group was related to duration of convalescence rather than to antirheumatic therapy.

Ballistocardiogram in Patients During Convalescence.—Convalescent patients were divided into two groups: those with clinical evidence of organic heart disease and those without such evidence. Forty per cent of patients with rheumatic heart disease were found to have significant BCG abnormalities during the first three months of convalescence. The incidence of such abnormalities had decreased to 28 per cent between the third and sixth month and to 9 per cent beyond the sixth month. Thirty-nine per cent of patients without evidence of heart disease had BCG's of Grade 2 abnormality or greater during the first three months. This incidence decreased to 9 per cent during the second three months, and all were normal after six months (Table IV) (Figs. 1 to 3).

TABLE IV. RELATIONSHIP TO PRESENCE OF RHEUMATIC HEART DISEASE: PER CENT OF PATIENTS WITH ABNORMAL BCG'S FOLLOWING SUBSIDENCE OF RHEUMATIC ACTIVITY

	NO. OF PATIENTS	0-3 MONTHS (%)	3-6 MONTHS (%)	MORE THAN 6 MONTHS (%)
Rheumatic heart disease	52	40	28	9
No heart disease	38	39.4	9	0

Because of the high incidence of abnormal BCG's early in convalesence in patients without evidence of valvular deformity, an analysis was made of the presence of clinically evident carditis during the antecedent attack of acute

TABLE V. RELATIONSHIP TO PRESENCE OF CARDITIS DURING ANTECEDENT ATTACK: PER CENT OF PATIENTS WITH ABNORMAL BCG'S FOLLOWING SUBSIDENCE OF RHEUMATIC ACTIVITY

	NO. OF PATIENTS	0-3 MONTHS (%)	3-6 MONTHS (%)	MORE THAN 6 MONTHS (%)
Patients with carditis during acute attack	53	53	28	7
Patients without carditis* during acute attack	37	22	8	0

*No clinical evidence of cardiac involvement.

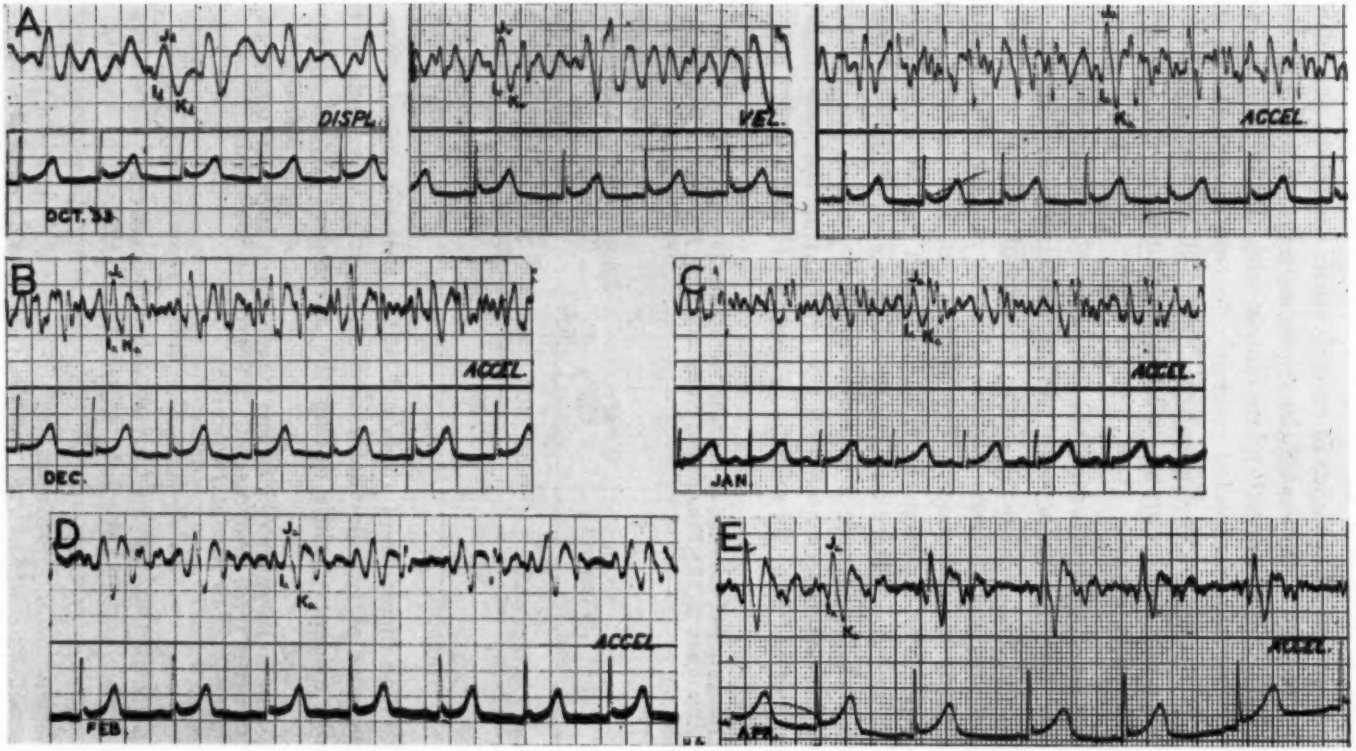

Fig. 1.—BCG course of H. G., acute rheumatic fever with active carditis. *A*, Acute stage (October, 1953). The displacement trace is near normal; the velocity and acceleration are abnormal. In acceleration the complexes are difficult to identify; most are of abnormal form and the trace is devoid of repetitiveness. A diastolic impulse (about 0.40 sec. after "R") is more consistent than the IJK. This phenomenon first described by Talbot and Scarborough diminishes progressively in succeeding months as the BCG complex becomes better defined. *B,C*, Early convalescence (2 and 3 months later). The acceleration trace is improved but still abnormal, R-I_a waves from 0.08 to 0.12 sec. and I_a-K_a from 0.08 to 0.14 sec. *D*, Late convalescence (4 months later). The systolic complexes have now become adequately repetitive but the I_a peak is still rounded and slow. *E*, Late convalescence (6 months later). Normal acceleration tracing. Small slur on the JK stroke.

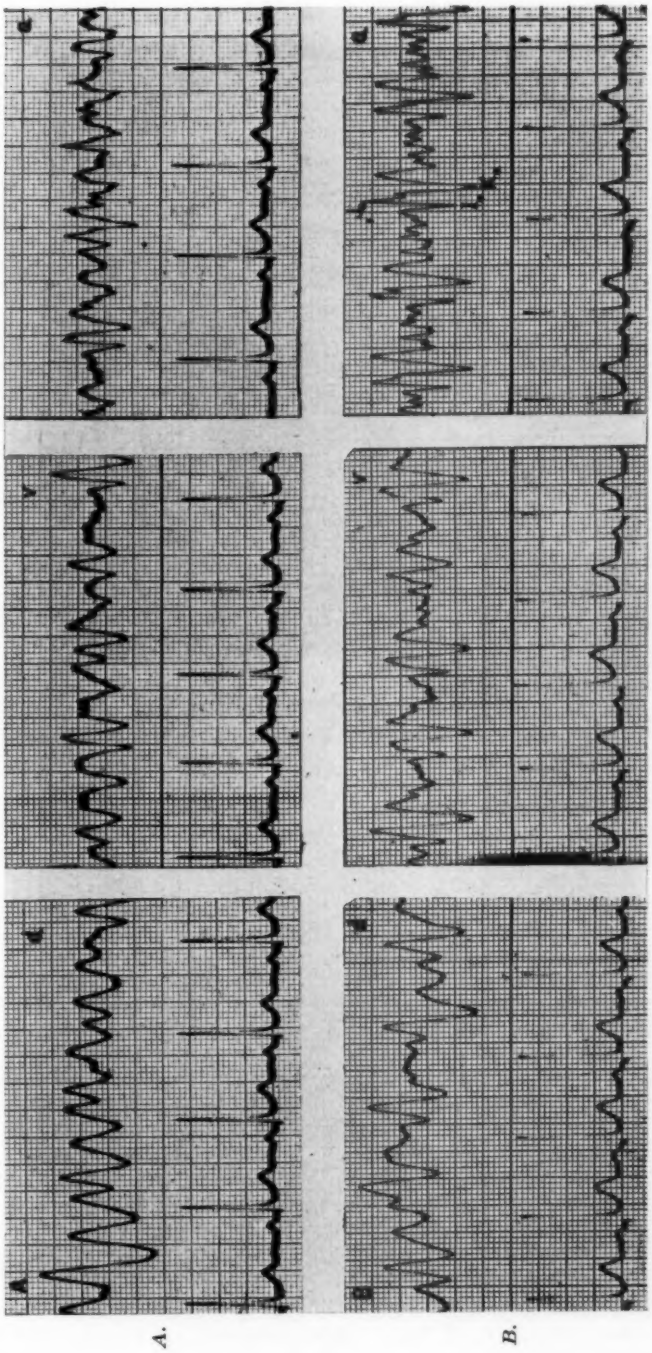

Fig. 2.—E.K. *A*, Early in convalescence from mild and short siege of rheumatic fever. The acceleration curve clearly defines the erratic high-frequency forces that make the tracing abnormal. These are crossed out on the displacement curve which appears smooth and rolling. *B*, Five months later, the acceleration curve is normal (in spite of the notch on the JK_a stroke). The *d* and *v* curves show some irregularities.

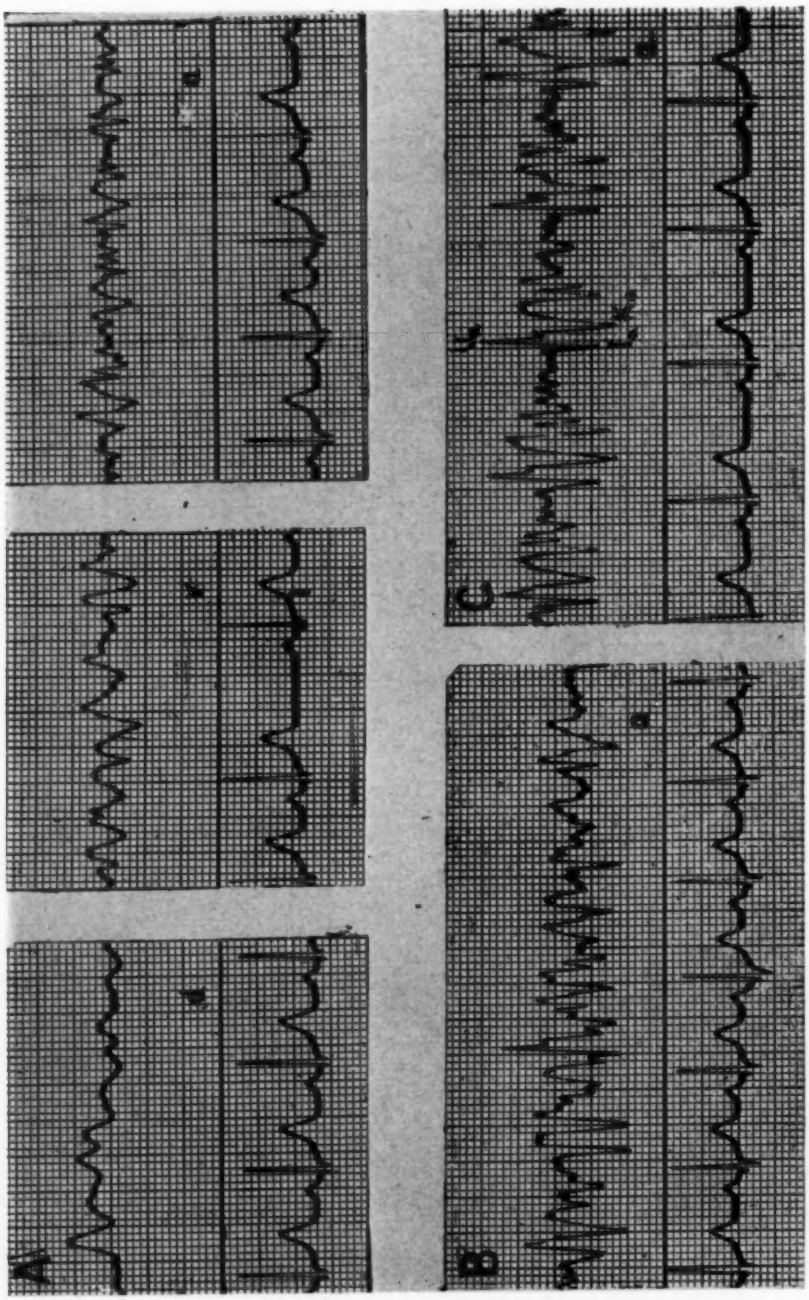

Fig. 3.—*J de R.* Active rheumatic fever without any clinical or laboratory evidence of cardiac involvement. *A*, During acute attack. Abnormal BCG. The displacement curve has a discernible and repeated IJK_d complex of low amplitude and slight irregularity. The complexes in velocity are of less consistent form. In acceleration the form is poor, and no successive complex is repetitive. *B*, Two months later in early convalescence. An occasional complex is now more sharply defined, but the majority are still irregular in form and nonrepetitive. *C*, Four months later, late convalescence. Grade 1, BCG. The notched JK_s stroke occurs frequently during convalescence. This tends to become less pronounced or to disappear later.

rheumatic fever. Evidence of antecedent carditis was considered to be the presence during the acute attack of at least one of the following: (1) appearance of an organic murmur (or a significant change in murmur where organic valvular disease was already present), (2) heart failure, (3) pericarditis, (4) change in heart size.

Patients with carditis during the acute episode had a higher percentage of BCG abnormality during convalescence than those without carditis. The persistence of the BCG abnormality was also more prolonged when carditis had been present during the acute attack (Table V).

DISCUSSION

This study was undertaken to determine empirically whether a correlation exists between the stages and severity of rheumatic fever and the deviation of the ballistocardiogram from normal. Experience with the acceleration ballistocardiogram is limited, and the criteria for abnormality are not yet well established. The classification employed has designated as "abnormal" a Grade 2 record as defined previously. Such variations in the pattern of the record have been observed in less than 2 per cent of the total normal group studied so far. Variations graded as 1 were not classified as abnormal even though such changes may have physiologic and pathologic significance. Those records graded as 2 or 3 are therefore likely to represent marked variations from the normal rather than borderline abnormalities.

Ultimately all of us came to reading the acceleration curve to the exclusion of displacement and velocity. The reasons for this were: (1) The acceleration curve faithfully reproduced the BCG at any pulse rate. Displacement and velocity records became deformed as the rate exceeded 100 beats per minute (Fig. 4). (2) It was not influenced by such factors as the body index (the ratio of weight to the square of height). Displacement records are particularly affected by the physical characteristics of the patient. (3) On the same patient it most consistently reproduced the same wave form in serial tracings. (4) The base line of the acceleration curve was flat and free of respiratory weaving even during deep respirations. It was not necessary to train children to breathe in any specific manner. Errors due to improper breath holding and unintentional Valsalva and Müller maneuvers are eliminated. (5) Body acceleration can be demonstrated mathematically to be most closely related to the force exerted by the heart in the system employed.[11]

In the group of 100 proved noncardiac children studied in this series, BCG abnormalities were not present by these criteria. In fifty unselected normal school children, 4 per cent were found abnormal. The incidence of abnormal displacement BCG's determined in a large series of healthy young soldiers has been reported as 7.2 per cent.[3] The frequency of abnormal BCG's in apparently healthy adults appears to increase with age.[8-10] Because patients with rheumatic fever studied in this series were below the age of 16 the high percentage of BCG abnormalities observed would appear to be significant.

As might be expected, the data indicated the highest correlation between the presence of congestive heart failure and the degree of BCG abnormality.

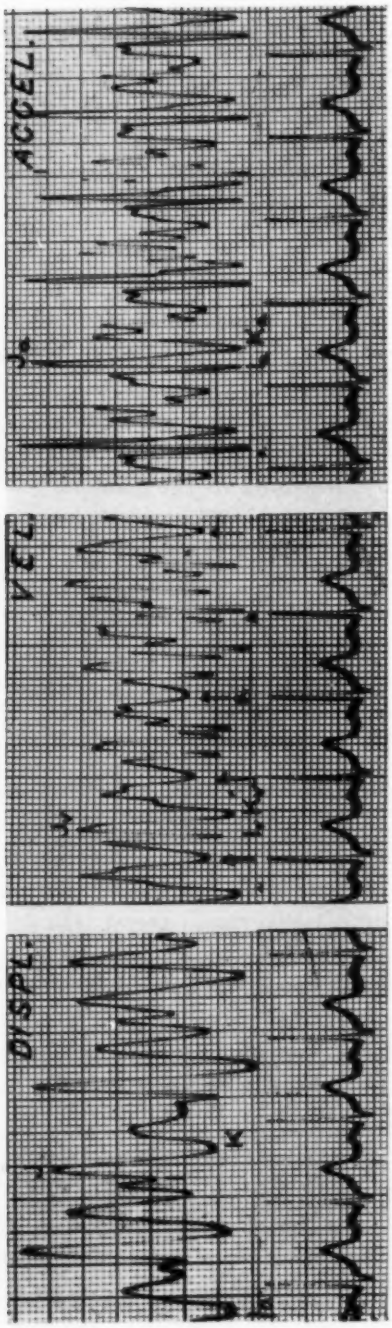

Fig. 4.—Sinus tachycardia, rate 120. The displacement and velocity curves offer some difficulty in the exact determination of their grading. The acceleration tracing is sharp, clearly defined, and unquestionably Grade 1.

Patients who had acute rheumatic fever associated with severe carditis showed this correlation most consistently. When mild carditis, unassociated with heart failure, was present, BCG abnormalities were less frequent. Patients who had other manifestations of frank rheumatic fever (polyarthritis, chorea, etc.) without clinically evident carditis had a still lower incidence of BCG abnormality.

The BCG did not appear to reflect antirheumatic therapy per se. There did appear to be a correlation between the disappearance of clinically evident carditis and BCG improvement. The BCG remained abnormal in patients with persistent chronic carditis and heart failure.

The rate of improvement of the BCG after subsidence of the acute attack appeared to be mainly a function of the duration of convalescence. Grade 2 and 3 abnormalities usually disappeared within six months even in those patients who had persistent valvular deformities or cardiac chamber enlargment except when such enlargement was marked or when obvious limitation of cardiac reserve was present. The most significant factor influencing the incidence and persistence of BCG abnormalities during convalescence appeared to be the presence of clinically apparent active carditis in the recent attack. It is of special interest that at times BCG abnormalities were observed during the acute attack and early convalescence in patients who had neither clinically evident acute carditis nor manifest rheumatic valvular heart disease. These BCG abnormalities disappeared after an extended period of convalescence.

It cannot be stated, however, that the BCG abnormalities observed in such patients necessarily reflect specific rheumatic involvement of the myocardium. A control group of clinically ill and bedridden nonrheumatic patients has not been studied to exclude possible influence of nonspecific factors upon the BCG.

SUMMARY

Ballistocardiograms of body acceleration, velocity, and displacement were recorded serially in 170 children, ranging in age from 6 to 15 years, during various stages of acute rheumatic fever and during convalescence. Similar records were obtained from a control group of 150 children. Changes in the acceleration ballistocardiogram designated as grossly "abnormal" were encountered in 1.3 per cent of the total control group.

There was a direct relationship between the severity of acute rheumatic carditis and the incidence and degree of ballistocardiographic abnormality. The incidence of grossly abnormal ballistocardiograms decreased as the acute rheumatic attack subsided. During treatment with either cortisone or salicylates, the ballistocardiogram appeared to reflect the cardiac status of the patient rather than the symptomatic response to the anti-inflammatory effects of therapy.

During the first few months of convalescence, patients with the highest incidence of abnormal ballistocardiograms were those who had had clinically evident carditis during the acute stage of the disease. Within six months, the incidence of gross abnormalities in the BCG's in this group decreased significantly. Patients without apparent carditis during the acute stage of the disease had fewer abnormal BCG's during the first three months of convalescence. All reverted to normal after six months. Progressive improvement in the ballisto-

cardiogram occurred despite the persistence of valvular deformity except in some patients with marked cardiac enlargement.

This study indicates that marked acceleration BCG changes occur frequently during the acute stages of rheumatic fever, when rheumatic carditis is clinically evident. When clinical manifestations of carditis are absent such changes appear less frequently and are less marked. During convalescence virtually all abnormalities disappear by the end of six months except in those patients whose cardiac reserve is limited by persistent chronic rheumatic carditis or advanced rheumatic heart disease.

The acceleration BCG has many advantages over previously described methods for the measurement of body motion. The absence of quantitative criteria to determine the range of normal variation compels dependence upon subjective impressions which at present impose a serious limitation upon the immediate clinical application of the method. The results of this study, however, justify further investigation of the use of the acceleration BCG to detect myocardial involvement in patients with rheumatic fever.

SUMMARIO IN INTERLINGUA

Le objectivo principal del presente studio esseva determinar si le ballistocardiogramma es de valor in le detection de affectiones cardiac in casos de febre rheumatic.

Le comparation del ballistocardiogrammas obtenite ab omne le patientes al tempore de lor admission a "Irvington House" con illos obtenite al tempore de lor dimission revelava al initio un frequentia de 46 pro cento de ballistocardiogrammas significativemente anormal e al fin de un periodo median de septe menses de observation un correspondente frequentia de 10 pro cento.

Al tempore del admission le frequentia de ballistocardiogrammas anormal variava ab 90 pro cento inter le patientes con clar carditis rheumatic a 18 pro cento inter illes con solmente isolate manifestationes de febre rheumatic. Al tempore de lor dimission omne le patientes habeva ballistocardiogrammas normal excepte illes qui habeva congestive insufficientia cardiac durante le attacco.

Le datos presentate indica un directe relation inter le frequentia de anormalitates ballistocardiographic e le severitate del activitate rheumatic.

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BALLISTOCARDIOGRAPHIC STUDIES IN PATIENTS WITH PROBABLE MYOCARDITIS

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IT IS becoming increasingly evident that myocarditis, a frequent accompaniment of rheumatic fever, may complicate infectious, viral, and collagen diseases. Four years ago,[1] we observed a patient four weeks after "recovery" from acute tonsilitis and migratory joint pains. Fatigue and tachycardia persisted. The physical examination and electrocardiogram were normal, but the erythrocyte sedimentation rate was rapid. The ballistocardiogram showed an abnormal pattern. One week later, a Grade 1 mitral systolic murmur was noted; the ballistocardiographic abnormality persisted and the electrocardiogram showed P-R prolongation. After four weeks, the murmur was no longer evident, and the electrocardiogram and erythrocyte sedimentation time were normal. However, the ballistocardiogram did not return to normal until the eighth week, at which time the patient was free of symptoms and returned to work.

Since this experience, we have subjected fifteen cases recovering from rheumatic fever to serial ballistocardiographic studies and have found abnormal findings in all subjects, except in five below the age of 20. We extended our investigations to patients recovering from infectious and viral diseases, to cases of disseminated lupus erythematosus, scleroderma, to subjects suffering from serum or drug reactions, and to those with acute diffuse glomerulonephritis or the nephrotic syndrome.

HOW DOES MYOCARDITIS ALTER THE BALLISTOCARDIOGRAM

Rothschild and his associates[2] have shown that the occurrence of heart failure in the first five decades of life in individuals who have a valvular defect can be attributed, in the majority of instances, to an active infection of the myocardium rather than to the mechanical defect.

Lenel and associates,[3] in their clinicopathologic study of 300 cases of rheumatic heart disease, reported that the myocardial lesions and not the valvular deformities play the predominant role in rheumatic heart disease. They noted that acute myocarditis was the cause of heart failure and deaths in all cases of acute rheumatic fever. A good percentage of the patients over 50, who had

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severe valvular deformities, were without cardiac symptoms during life. Extensive fibrosis of the myocardium was a more constant finding than severe valvular deformities in patients developing chronic heart failure.

Dock and associates[4] believe that in most cases of myocarditis, changes in the ballistocardiogram are related to incomplete systolic ejection, which leads to a rise in left ventricular diastolic pressure, a rise in pulmonary arterial pressure, which in turn causes increased resistance to right ventricular ejection. These phenomena may develop only after exercise. In subclinical failure, with a minimal rise in pulmonary resistance, the ballistocardiogram may show a decrease in the I-J stroke and an increase in inspiratory-expiratory variation. As failure becomes more advanced, return flow to the heart is decreased and the rise in venous pressure augments the speed of diastolic filling of the ventricles. The ballistocardiogram shows large H and/or L waves; I is reduced in size and may be absent so that H-J fuse into a plateau. As the heart dilates and gallop rhythm becomes manifest, tall H and L waves may dominate the trace. In advanced failure, diminutive L waves and tall N waves give a notched appearance to K-N. These diastolic waves are usually more prominent when recorded in the lateral plane.[5] That congestive heart failure rather than valvular disease is responsible for the ballistocardiographic change is proved by the effectiveness of digitalis in improving the ballistocardiogram toward normal,[4] and by improvement in the trace following recovery, while signs, due to organic valvular lesions, persist or may appear at a later day.

IMPORTANCE OF SERIAL TRACES, THE EXERCISE TEST, AND THE INFLUENCE OF AGE

In five subjects below the age of 18, we noted normal displacement ballistocardiograms in the presence of clinical evidence of myocarditis. Dock[6] is of the opinion that presbycardia accounts for the phenomenon; that the heart of youth, free of involutional changes, is better able to carry on its function in the presence of myocarditis than those over 20, at about which age presbycardia probably begins. However, in adolescents, where serial traces were done, comparative studies of ballistocardiograms taken before and after recovery will often show striking quantitative changes. Low I-J waves, with relatively tall H and L waves, may be present for weeks after clinical "recovery."[4]

In a high proportion of our subjects between the ages of 20 and 35, abnormalities in the ballistocardiogram appeared only after the light exercise test (see Fig. 8 of Reference[7]).

The ballistocardiographic abnormalities seen in subjects with probable myocarditis are not specific. Similar abnormalities could be caused by old myocardial scarring or by coronary artery disease, especially in subjects over 40 years of age. However, where the ballistocardiogram has returned to normal or to Grade 1 (according to the classification of Brown and associates),[8] it is quite probable that myocarditis was responsible for the abnormalities in the ballistocardiogram during the acute episode.

MYOCARDITIS COMPLICATING OTHER DISEASES

Ballistocardiographic studies at rest and after exercise were done on patients recovering from febrile diseases; in most instances, there were no clinical indications of cardiac disease. In eighteen cases of infectious mononucleosis, eight (44 per cent) showed abnormal traces. Houck[9] states that while autopsy records occasionally may show focal infiltrations of abnormal lymphocytes, a higher incidence of electrocardiographic abnormalities (5 to 50 per cent) is being reported in infectious mononucleosis.[10] Custer and Smith,[11] in their study of post-mortem findings in infectious mononucleosis, noted six instances of aggregates of lymphocytes sparsely distributed within the myocardium in small numbers beneath the endocardium. In one patient who died of an accident shortly after recovery from infectious mononucleosis, extensive residual areas of necrosis were found.

In five cases of disseminated lupus erythematosus, four showed ballistocardiographic abnormalities; in three, remission was effected by cortisone and the ballistocardiograms returned to normal. Two of these subjects had definitive electrocardiographic changes.

Biegelman and his associates[12] studied fifteen patients with scleroderma. Eleven had systolic murmurs. Gallop rhythm and multiple arrhythmias were observed, and in six marked cardiomegaly was demonstrated. Five of the patients died; all five showed microscopic evidence of myocardial fibrosis; four showed pericardial thickening, and four showed endocardial and valvular fibrosis. In our four cases of scleroderma, three showed ballistocardiographic abnormalities. Electrocardiographic abnormality was noted in the one case with advanced systemic disease.

Ballistocardiographic evidence of myocardial functional impairment was also found in patients with serum sickness (one of two cases) and severe penicillin reaction (two of six cases). The electrocardiograms of all these patients were normal.

It is interesting to note that in six cases of acute diffuse glomerulonephritis (aged 19, 24, 27, 37, 39, and 44), all showed ballistocardiographic abnormalities with the exception of the 19-year-old patient. Peters[13] made the observation that congestive heart failure is a feature of most cases of acute glomerulonephritis. In five instances, the ballistocardiogram ultimately returned to normal, leaving no doubt that myocarditis had been present. There were no electrocardiographic abnormalities in any of these cases. In three cases (aged 18, 28, and 36) with the nephrotic syndrome, normal ballistocardiograms were obtained initially and in follow-up studies.

Roehm[14] recently reported a case of trichinosis showing ballistocardiographic evidence of myocarditis. We studied a similar case who showed marked ballistocardiographic abnormalities. Cortisone was given for two weeks; the ballistocardiogram returned to normal after the fourth week.

In studies on eleven patients convalescing from pneumonia, ballistocardiographic abnormalities were noted in three of the subjects. In two, the ballistocardiogram returned to normal within three weeks.

SUMMARY AND CONCLUSION

While the ballistocardiograph does not furnish a pattern distinctive of myocarditis, ballistocardiographic abnormalities may be the first indication of myocardial functional impairment.

Myocarditis in adults is frequently associated with an abnormal ballistocardiogram. In children and in adolescent subjects, the significance of the initial traces may become apparent only after comparison with the recovery ballistocardiograms. In subjects between the ages of 20 and 30, where myocarditis is suspected, the light-exercise test may bring out abnormalities in the ballistocardiogram where the resting trace was normal.

Abnormal ballistocardiograms, as evidence of probable myocarditis, have been observed in rheumatic fever, disseminated lupus erythematosus, scleroderma, trichinosis, acute diffuse glomerulonephritis, in patients convalescing from infectious mononucleosis and pneumonia and in instances of serum or drug sensitivity reactions.

It is our experience that during the active stage of myocarditis, abnormal ballistocardiographic patterns are more frequent than electrocardiographic evidence of disease.

The discovery of an abnormal ballistocardiogram in a patient with atypical joint and muscle pains or fever of undetermined origin, fatigability, tachycardia, and a high erythrocyte sedimentation rate may provide convincing proof of myocarditis, where all other studies have failed.[4]

Ballistocardiography should be regarded as an important supplement in the observations of patients ill or recovering from rheumatic fever, collagen diseases, infectious and viral diseases, and acute glomerulonephritis. It serves as a guide in detecting myocarditis and as an index of complete recovery.

CASE REPORTS

CASE 1.—F.S., a 34-year-old woman, complained of low-grade fever and migratory joint pains of three weeks' duration. Physical examination was negative; the electrocardiogram was normal. The erythrocyte sedimentation time was 32 mm. at the end of one hour. The basal ballistocardiogram (*A*)* showed complexes of low amplitude with relative prominence of the L waves (Fig. 1).

The patient was treated with salicylates, with little improvement. After four weeks (April 20, 1952), no murmurs were evident; the electrocardiogram showed a P-R of 0.12 sec. and a Q-T of 0.4 sec. The erythrocyte sedimentation time was 20 mm. The basal ballistocardiogram (*B*) was of the Grade 3 pattern, with relatively tall H and L waves and short I-J waves.

She was treated with cortisone for the next four weeks. Arthralgia and fever abated and the sedimentation time became normal. The electrocardiogram was normal. A Grade 1 systolic murmur was evident. The ballistocardiogram, at rest (*C*), and after light exercise (*D*), was Grade 2, with normal complexes seen in the inspiratory phase.

Cortisone was continued for two months and then tapered off. By September 15, 1952, no murmurs were evident and the electrocardiogram was normal. The basal ballistocardiogram (*E*) was normal; after light exercise (*F*), notched K waves may be noted.

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*The upper trace is the ballistocardiogram; the lower, a pulse trace obtained from the left radial artery. Grades 1, 2, 3, and 4 follow the classification of Brown and associates.[3]

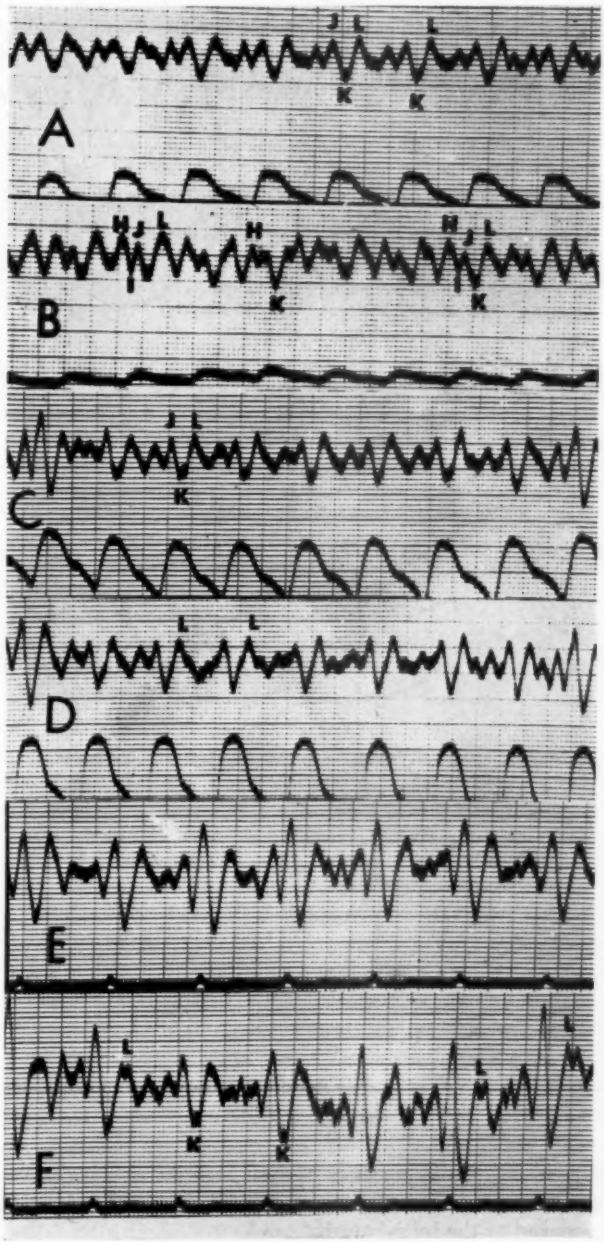

Fig. 1.—Case 1. Rheumatic fever.

CASE 2.—E.K., a 38-year-old woman, suffered from joint pains for four months, and fever for two months. The electrocardiogram was normal, and there were no cardiac murmurs. Albuminuria was noted and bone marrow smears showed characteristic lupus erythematosus cells. On January 11, 1954 (Fig. 2), the basal ballistocardiogram (*A*) showed tall L waves and after light exercise (*B*) fused H-J waves, notched J waves and tall N waves were noted. Cortisone in large doses resulted in a remission so that after three months, she was able to return to work; the basal (*C*) and the exercise (*D*) ballistocardiograms were normal.

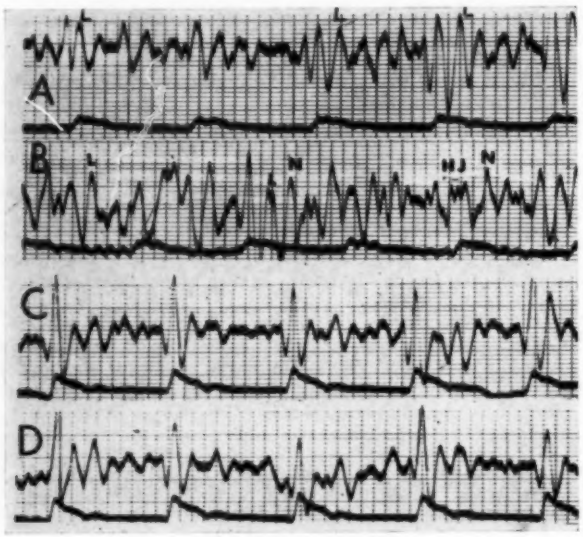

Fig. 2.—Case 2. Disseminated lupus erythematosus.

CASE 3.—J.W., a 32-year-old electrician, an athlete, received penicillin for a carbuncle of the neck. Two days later, he developed swollen painful joints, fever, and urticaria. He was treated with antihistamines, with no response. He was seen in consultation one week later (February 11, 1953); clinical examination and the electrocardiogram were normal. The resting ballistocardiogram (Fig. 3) (*A*) showed Grade 1 respiratory variation and tall L waves; after light exercise (*B*), Grade 2 respiratory variations were noted, with expiratory fused H-J waves.

He responded well to cortisone, and after ten days was symptom free. He felt well enough to return to work, and on March 2, 1953, the resting (*C*) and exercise (*D*) ballistocardiograms were normal.

This case illustrates: (1) the importance of light exercise in bringing out abnormalities due to impaired myocardial function; and (2) the changes in the amplitude of the complexes of the recovery trace as compared to the initial study.

CASE 4.—M.G., a 30-year-old clerk, was ill for four weeks with infectious mononucleosis. Following "recovery," fatigue continued. He was seen two weeks later (February 19, 1952); clinical examination and the electrocardiogram were normal. The erythrocyte sedimentation time was 24 mm. The resting ballistocardiogram (Fig. 4) (*A*) showed little respiratory variation but tall L waves. After light exercise (*B*), blunting of the J peaks and fused H-J waves may be seen in the expiratory complexes.

He was put to bed for two weeks, and his activity was limited for another two weeks. On April 24, 1952, he felt well enough to go to work. Examination was negative; the sedimentation time was normal. The resting (*C*) and light exercise (*D*) ballistocardiograms were normal.

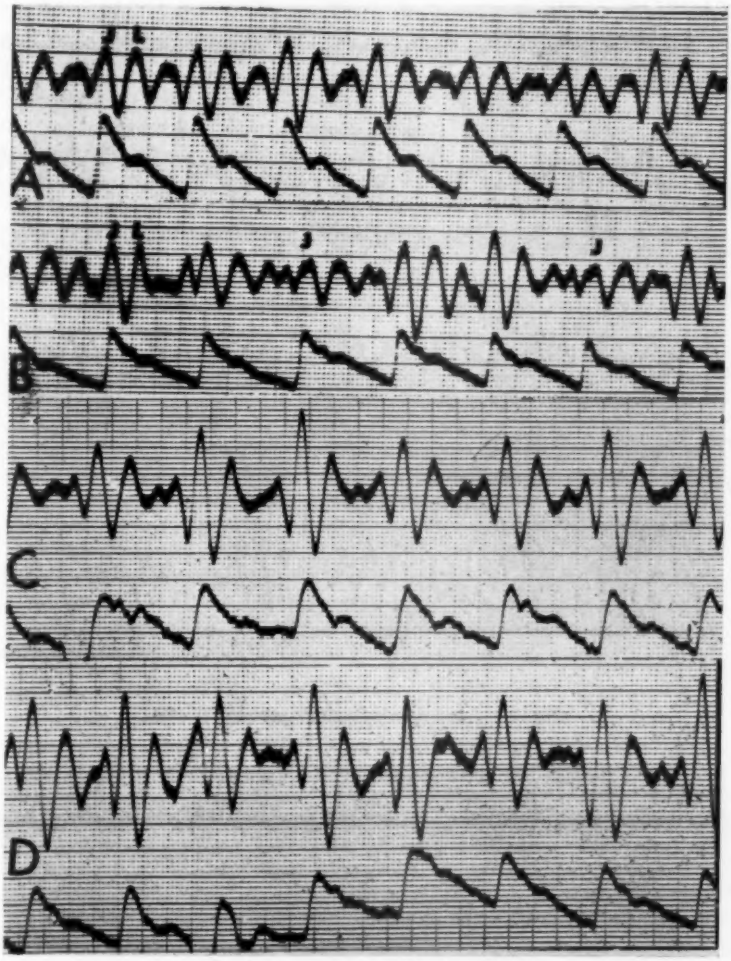

Fig. 3.—Case 3. Penicillin sensitivity.

CASE 5.—R.H., a 40-year-old housewife, developed acute glomerulonephritis two weeks after an upper respiratory infection (November 30, 1952). Edema, hypertension, and azotemia developed, and she was admitted to the hospital on December 7, 1952. The heart was enlarged and a protodiastolic gallop was evident. The blood pressure ranged from 175/110 to 195/125 mm. Hg. There was a 4-plus albuminuria, the urea N was 48 mg. per cent, and the hemoglobin was 72 per cent. The electrocardiogram showed left ventricular hypertrophy. The ballistocardiogram (Fig. 5) (*A*) was Grade 4.

She did not respond to bed rest and dietary regimen. Because the edema was worsening, a trial of cortisone for ten days was undertaken. On March 10, 1953, there was no apparent clinical or laboratory improvement. The resting ballistocardiogram (*B*) showed a Grade 3 pattern.

Digitalis was begun and after two weeks a second course of cortisone was given, with some improvement. Three subsequent courses of cortisone followed (10 days of cortisone therapy, 14 days without cortisone). Digitalis was continued.

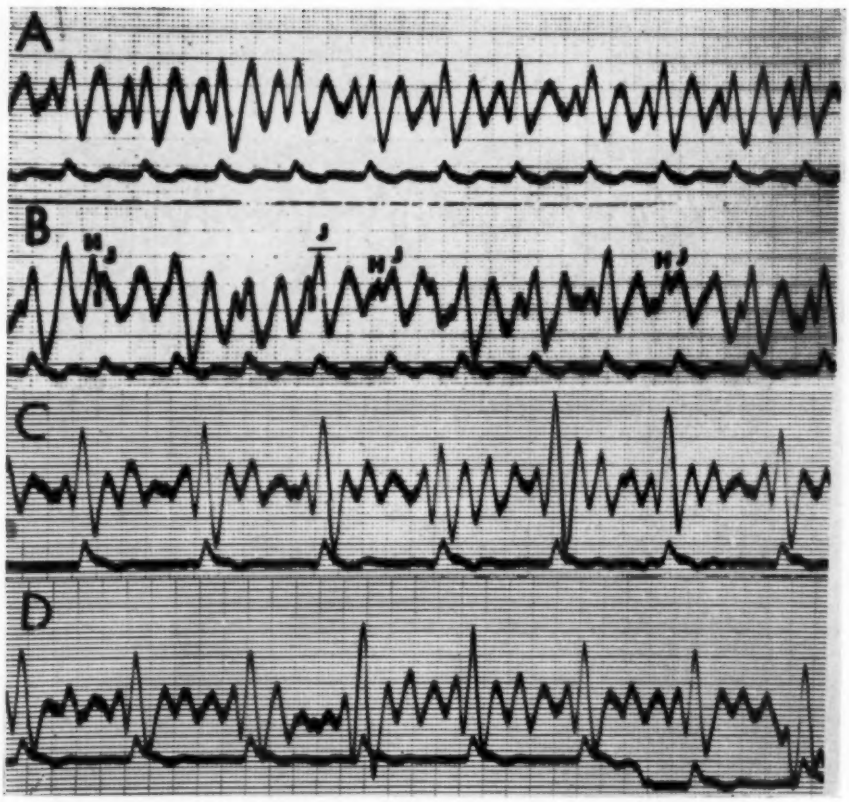

Fig. 4.—Case 4. Infectious mononucleosis.

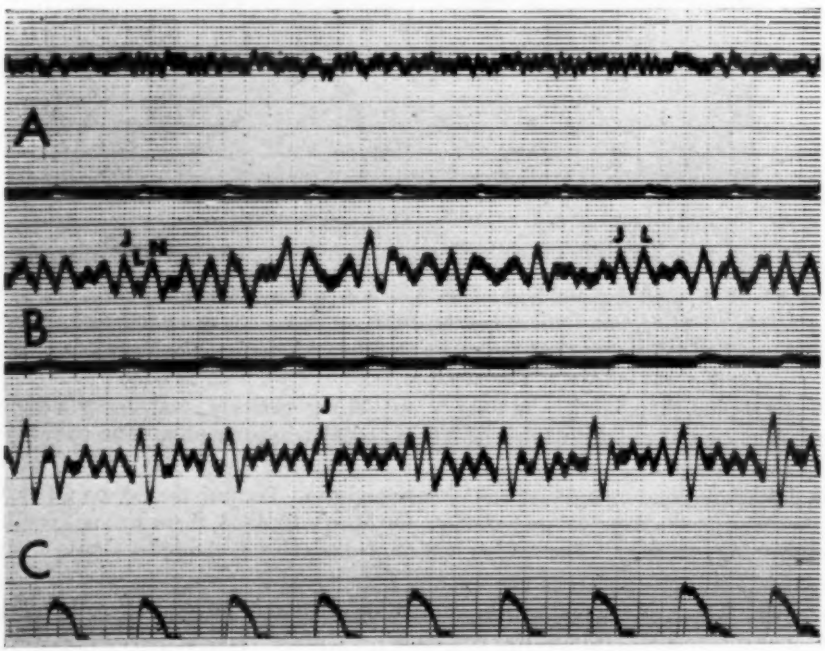

Fig. 5.—Case 5. Acute glomerulonephritis.

On June 15, 1953, the blood pressure was normal, and no edema was evident. The heart was not enlarged; the electrocardiogram showed left ventricular hypertrophy. There was no azotemia but a heavy trace of albumin was present in each urinalysis. The basal and the exercise (*C*) ballistocardiograms were normal except for one notched J wave.

SUMMARIO IN INTERLINGUA

In 1950 nos obteneva ballistocardiogrammas anormal ab un patiente recovrante de un accesso de tonsillitis e de penas del articulationes. Isto faceva nos suspectar myocarditis. Ab ille tempore studios ballistocardiographic esseva executate pro 70 patientes suffrente o recovrante de febre rheumatic, disseminate lupus erythematose, scleroderma, trichinosis, glomerulonephritis diffuse acute, mononucleosis infectiose, pneumonia, morbo seral, o reactiones penicillinic.

Ben que le ballistocardiographo non produce un configuration specific de myocarditis, illo pote esser le prime medio pro deteger un disturbation functional myocardiac quando myocarditis es suspectate. In adultos un significative numero de ballistocardiogrammas anormal esseva obtentite. In juveniles e adolescentes il non es infrequente que le signification de tracias initial de anormalitates deveni apparente solo post lor comparation con le ballistocardiogramma de recovrage. In individuos de inter 20 e 30 annos de etate, le experimento a leve exercitios pote relevar anormalitates in casos in que le registration in stato de reposo esseva normal.

The authors wish to express their appreciation to Dr. William Dock for his invaluable assistance in all phases of this study.

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DETERMINATION OF THE ELECTRICAL CENTER OF VENTRICULAR DEPOLARIZATION IN THE HUMAN HEART

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INTRODUCTION

DETERMINATION of the electrical center of ventricular depolarization is a basic problem in electrocardiography involving the establishment in three dimensions of the location of an equivalent current dipole which produces approximately the same body-surface potentials as the actual ventricles. The anatomic location within the heart of this equivalent dipole is, by definition, the center of the ventricles, insofar as the QRS complex is concerned. Many parameters affect body-surface potentials produced by electrical activation of heart muscle. Some of these are torso shape, posture, state of respiration, electrical inhomogeneities within the body, and anatomic location of the heart. The most influential factor is the anatomic location of the equivalent dipole; this has been established by experiments on torso models[1] and normal human subjects[16] and is substantiated on theoretical grounds.[2]

Although the true role of dipole location has not been clearly recognized in the past, efforts have been made to determine the electrical center for other reasons; for example, to obtain an indifferent reference electrode with which to explore areas of the body surface believed to exhibit effects owing to anatomic proximity to the heart.[3,4] While these local effects contribute only about 5 per cent to the QRS complex in normals,[5,6] it has not been firmly established whether they become significantly larger in certain types of heart disorders, but evidence indicates that local effects remain reasonably small in many abnormal cases.[5] Even if localized potentials were completely nonexistent, the electrical center of the heart would remain as the most important parameter in electrocardiography, and it is pertinent, therefore, to investigate its anatomic location. A terminal whose potential is very nearly equal to the heart-dipole mid-potential may also be determined after the dipole location has been established.

The best known and a widely used approximation to such a terminal, proposed by Wilson and associates,[7] is based on a theoretical analysis of a centric dipole in a homogeneous conducting sphere and is formed by connecting three

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equal resistors from the standard limb electrodes to a common junction, called the Wilson central terminal. Many efforts have been made to measure the degree to which the Wilson central-terminal potential approximates that of the heart-dipole mid-potential, but most of the work is subject to criticism and has not led to definitive results. For example, most immersion experiments[8-11] have suffered from the defect of extending the conducting medium beyond its normal body-surface boundaries, thus altering the current field within the body and, of course, the concomitant limb potentials. Moreover, in these experiments the techniques of measurement have been inadequate; body-surface potentials, diminished in amplitude as a result of the immersion, yield central-terminal potentials which are so small as to be barely discernible using the ordinary electrocardiograph.[11] It is hardly to be expected that the Wilson central terminal should have negligible error since the body is not spherical in shape and primarily because the heart dipole is not centrically located.[1,2] The Wilson central-terminal error is revealed as a consequence of the present method for determining the electrical center of the human heart. This error, directly measurable on the intact subject, will be shown to agree closely in both shape and amplitude with theoretical and torso model predictions. More important, the anatomic location of the heart center is also established by this work and constitutes the really vital information concerning the electrical center.

Determination of the Wilson central-terminal errors and establishment of a more accurate indifferent electrode are merely by-products of the present study, having more historical interest than pertinence to the basic problems in electrocardiography. Several more significant reasons for determining the electrical center of the heart are:

1. Body-surface potentials are so sensitive to the location of the equivalent heart dipole that entirely different electrocardiograms can result in two individuals with identical heart behavior, but different heart location. Obviously, accurate studies must correct for this location effect in evaluating the electrocardiogram.

2. Accurate determination of the heart vector can be carried out after the electrical center of the heart has been established anatomically and is an essential step in the critical evaluation of the fidelity of systems of vectorcardiography proposed for the human subject.

3. The role of human body inhomogeneities may be evaluated quantitatively by comparing human body wave forms with those produced on a homogeneous model of the human subject, but it is essential to know accurately the location of the center of electrical activity of the human heart to carry out such comparisons.

4. The pronounced influence of heart-center location indicates that attempts to correlate anatomic and electrical orientation of the heart are extremely limited unless the heart location is known and taken into account properly.

These and other objectives show the vital role played by the heart center and serve to illustrate its fundamental importance in establishing a sound basis for understanding the electrocardiogram.

A method recently presented[12] for determining the electrical center of the heart appears to be sound in principle but involves an extreme amount of experimental effort and lengthy data analysis. Moreover, its accuracy has not been stated. The method to be presented here requires 7 to 10 hours of experimental time on a given subject, and an estimate of the accuracy of the determination may be made readily. Data may be analyzed conveniently using a geometric technique. The method is based on a unique property of the anatomic line around the chest which lies in the transverse plane of the equivalent dipole; namely, contributions to the potential around this line by the head-to-foot dipole component are very small in comparison with those of the right-to-left and front-to-back components. The experimental procedure consists of determining mirror patterns of the QRS complex at the transverse level of the heart using a precision cancellation technique.[6] The cancellation data are systematically fitted to experimental torso model data in such a way as to determine the location of the equivalent dipole of ventricular depolarization to within an accuracy, in typical cases, of approximately ± 0.5 cm. anatomically and within about ± 0.2 mv. electrically. The method is rather generally applicable because it is relatively insensitive to the particular body build of the subject.

BASIS FOR THE METHOD

A general theory for dipole potentials produced in bounded three-dimensional conductors has been presented in detail.[13] The potential at any point on the boundary of a linear, resistive volume conductor containing a current dipole at any fixed point within the medium may be expressed in terms of the rectangular components of the dipole as

$$V = c_x p_x + c_y p_y + c_z p_z = \vec{c} \cdot p \qquad (1)$$

where

$$p = \vec{i} p_x + \vec{j} p_y + \vec{k} p_z$$

is the heart vector (dipole) whose components are functions of time;

$$\vec{c} = \vec{i} c_x + \vec{j} c_y + \vec{k} c_z$$

is the fixed unipolar vector whose components depend upon the medium characteristics, the dipole location, and the boundary point; and V is the potential of the boundary point with respect to the dipole mid-potential, arbitrarily assigned the value zero. A geometric intrepretation of Eq. (1) is given by the vector form in which V may be regarded as a scalar quantity arising from the projection of $\vec{p}$ onto the fixed vector $\vec{c}$, times the length of $\vec{c}$.

Experimental and theoretical studies of potentials produced on the boundary of various homogeneous volume conductors by an eccentric current dipole immersed in the conducting medium have revealed a useful characteristic which forms the cornerstone of this method of heart-center determination. This characteristic will be described for a torso-shaped boundary, but it also applies to many other boundary shapes. It can be shown[14] that the potential along the anatomic line around the chest at the transverse level of an eccentric equivalent dipole contains a very small contribution from the dipole component which

is perpendicular to the plane containing this transverse level. This may be expressed mathematically in terms of the coordinate system of Fig. 1 by stating that c_y is much smaller than c_x or c_z, whence

$$V_T \approx c_x p_x + c_z p_z \qquad (2)$$

where V_T is the potential at the transverse level of the heart center. Expressed

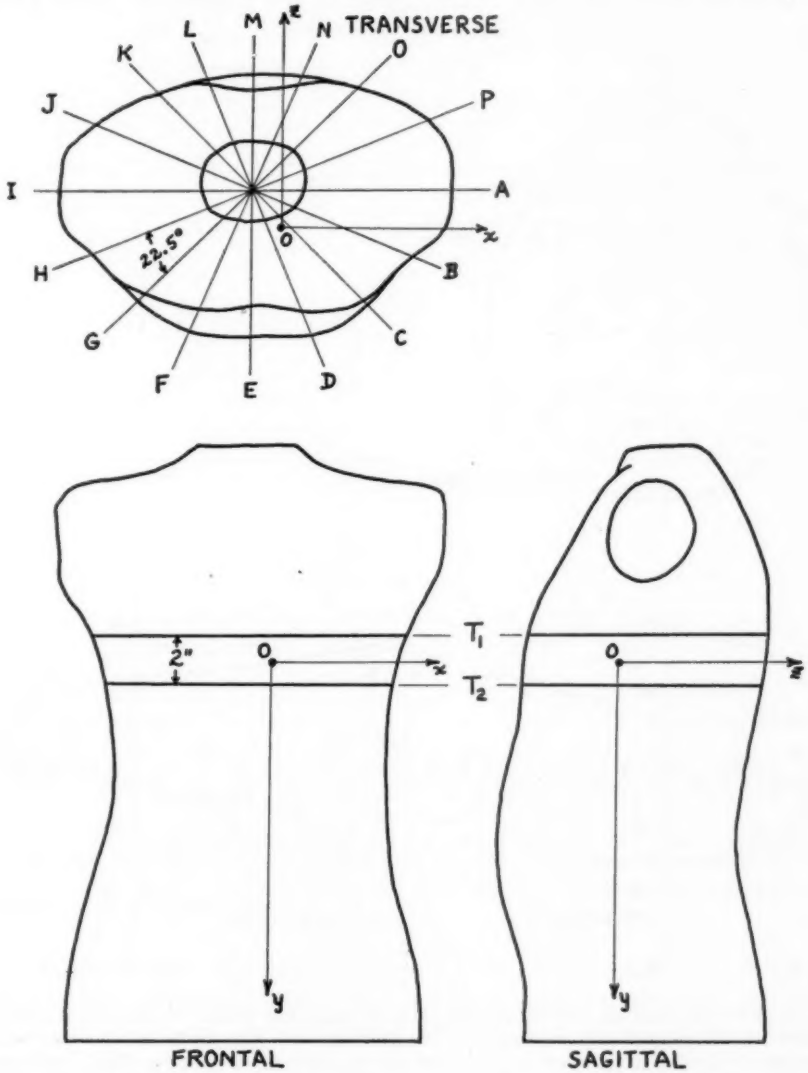

Fig. 1.—Frontal, sagittal, and transverse views of male torso illustrating method used to define anatomic points around the chest. Transverse levels T_1 and T_2 are, respectively, 1 inch above and below the heart center and are parallel to the xz-plane. Transverse radial lines spaced 22.5° apart emanate from the longitudinal axis of the trunk and determine sixteen points (A through P) at each transverse level. The transverse level midway between T_1 and T_2 is the critical level which is insensitive to the y-component of the dipole and is the level at which cancellation experiments are conducted. The origin of the rectangular coordinate system is at the heart center, point 0.

in another way, the mid-potential of an eccentric dipole oriented in the y-direction of Fig. 1 occurs approximately along the intersection with the boundary of a plane perpendicular to and passing through the dipole. This unique characteristic is not critically dependent on the anatomic contour of the chest nor upon the amount of dipole eccentricity within the range of variation encountered in human subjects. However, the potential distribution along this unique line is very sensitive to the location of the dipole in the transverse plane (xz-plane).

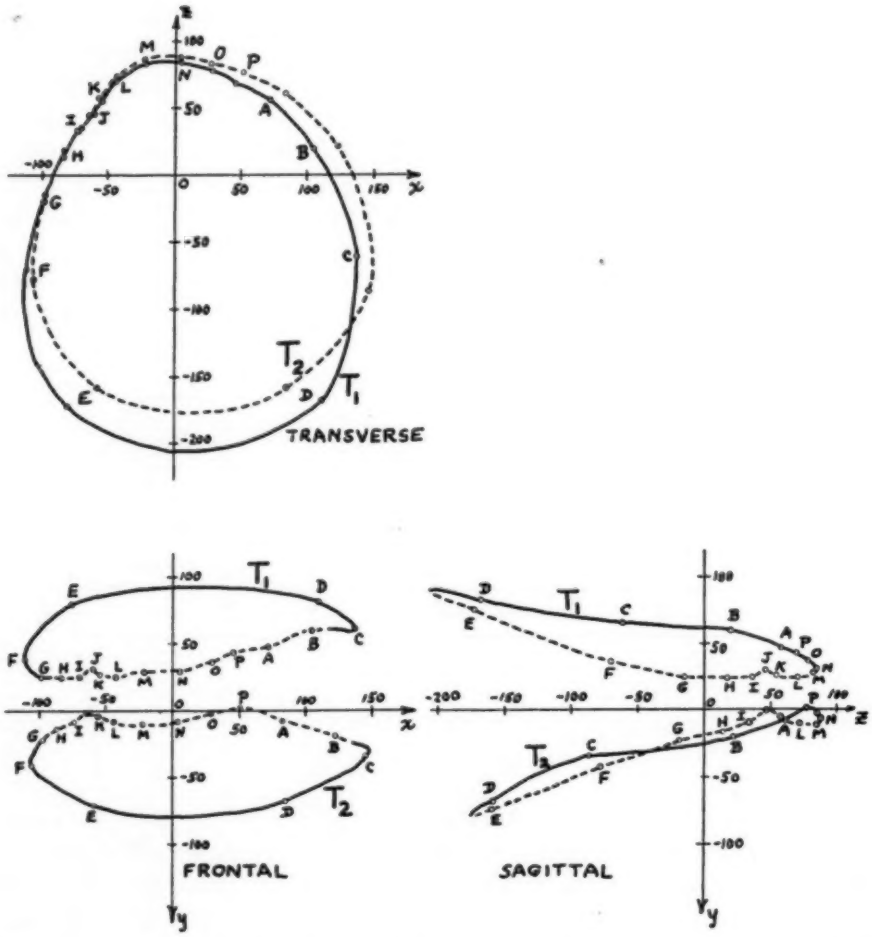

Fig. 2.—Frontal, sagittal, and transverse views of anatomic levels T_1 and T_2 as they appear in image space[14] for a homogeneous torso model. The heart center is at the origin of the coordinate system. Solid lines are in front of and dotted lines are behind the plane of the paper. The eccentric anatomic location of the dipole produces an outward bulge in image space around the precordium and a contraction of the right back points. Levels T_1 and T_2 are also greatly flared apart across the precordium. The transverse level midway between T_1 and T_2 lies very nearly in the xz-plane in image space, but the disposition of points A through P around this critical level is very similar to that shown for T_1 and T_2.

A geometric representation in image space of this property is contained, though not emphasized, in a previous publication[14] where anatomic level 6 may be seen to lie approximately in the plane containing the heart dipole. Image

data, applicable to results presented here, are given in Fig. 2 for the anatomic situation portrayed in Fig. 1. It may be seen that the two anatomic lines around the chest parallel to the transverse plane, T_1 and T_2, are not parallel to the xz-plane in image space. However, the transverse anatomic line which is precisely at the dipole level remains essentially parallel to the transverse plane in image space.

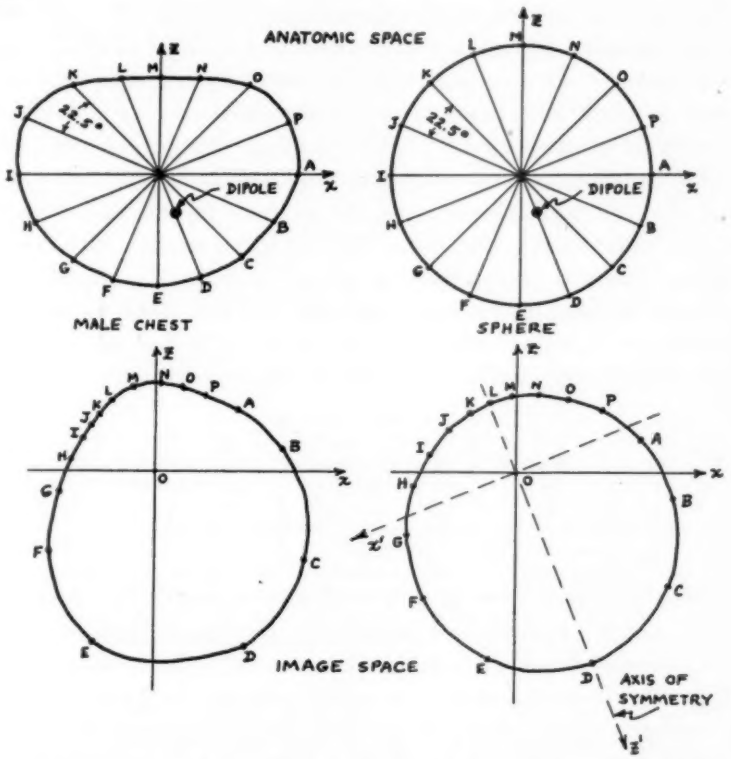

Fig. 3.—Image loops at the transverse level of an eccentric dipole are compared for a male chest boundary and a circular boundary. Each dipole is in a comparably eccentric location anatomically; f = 0.3. The two image loops may be seen to be surprisingly similar despite the gross difference in anatomic contour and illustrate the predominance of dipole location effects over boundary contour effects. Coordinates x'z' shown by dashed lines are those to which Eq. (3) applies. All four illustrations are cross sections of three-dimensional surfaces; results for two-dimensional cases with the same contours shown are quantitatively different.

The characteristic described suggests that mirror patterns should exist, using the four-electrode cancellation method previously described,[6] for electrode pairs located around the anatomic line whose plane contains the dipole midpotential. In principle, a comparison of the shape, amplitude, and distribution around the chest of these mirror patterns on the human subject with chest potentials produced in a torso model by dipoles in a variety of locations in the same transverse plane, permits a determination of the dipole location in the model which fits most closely the human data. This model dipole location may then be taken as the human equivalent dipole location. The matching process may be carried out entirely in terms of cancellation data using geometric constructions in image space, and it is unnecessary to analyze wave forms and amplitudes, which are less accurate, or to know the dipole components of the subject.

This process for determining the heart center tacitly assumes that cancellations will be obtainable. Since existence of cancellation substantiates the dipole hypothesis,[5,6] the method may be seen to possess a self-protective feature. If cancellations are not observed on a given subject, the method fails and this is precisely what is desired in such a case because lack of cancellation signifies nondipolar behavior and undermines the concept of electrical heart center.

Dipole location exerts such an over-riding influence on body-surface potentials that, fortunately, the anatomic contour of the chest of the human subject is not a critical factor. This means that the torso model data given in Appendix I may be used to carry out heart-center determinations for a wide variety of body builds without excessive error. To illustrate this for an extreme case the image loop corresponding to a circular anatomic line on the boundary of a spherical medium in the plane of an eccentric dipole may be compared with that obtained experimentally in the case of a human torso model with a comparably eccentric dipole. Such a comparison is given in Fig. 3. The image loop for the circular cross section is derived from Eq. (17) of a previous publication[15] with $\phi = 0$ and $p_x = -p \sin \psi$ and $p_z = p \cos \psi$. Coefficients c_x and c_z, which specify the image loop completely, are given in relative units by

$$c_x = \frac{1}{f \sin \Theta} \left[\frac{3f - 3f^2\mu + f^3 - \mu}{(1 + f^2 - 2f\mu)^{3/2}} + \mu \right]$$

$$c_z = \frac{1}{f} \left[\frac{1 - f^2}{(1 + f^2 - 2f\mu)^{3/2}} - 1 \right] \qquad (3)$$

where $f = b/R$, $R =$ sphere radius, $b =$ dipole eccentricity, and $\mu = \cos \Theta$. This result is a special example of a more general characteristic which shows the extreme importance of dipole location. It is not only the transverse level of the heart which is relatively insensitive to chest contour, but also the entire body build, while exerting some influence on body-surface potentials, is a much less significant factor than the heart location. Thus, if two individuals have quite different body builds but essentially the same relative dipole locations, the image surfaces of these two individuals will be very nearly the same for practically all points on their torsos. This has been demonstrated experimentally for male and female torso models of widely different proportions and contour.

EXPERIMENTAL PROCEDURE

A search for mirror patterns around the transverse level of the heart center may be carried out with precision using the four-electrode arrangement shown in Fig. 4. This cancellation system has been described in detail.[6] In this application electrodes 1 and 2 are fixed in location and tap a of the potentiometer connected between them is set to an arbitrary point, such as $m = 0.75$. Locations of electrodes 1 and 2 and of m determine an arbitrary reference potential for use in obtaining numerous mirror-pattern cancellations around the chest. It is not necessary that this reference potential be coincident with the dipole mid-potential in order to obtain cancellations[6] or to carry out the heart-center determination. However, it must be at the unique transverse level previously described, and it is desirable that it not be too eccentrically located in order to

obtain a reasonable spread of electrode locations where the best cancellations are found.

There are several methods for determining the anatomic level at which to set up electrodes 1 and 2. A trial and error procedure which can establish this level to within about ± 0.5 cm. anatomically is based on a study of right-arm and left-leg potentials in torso models for a wide variety of dipole locations.

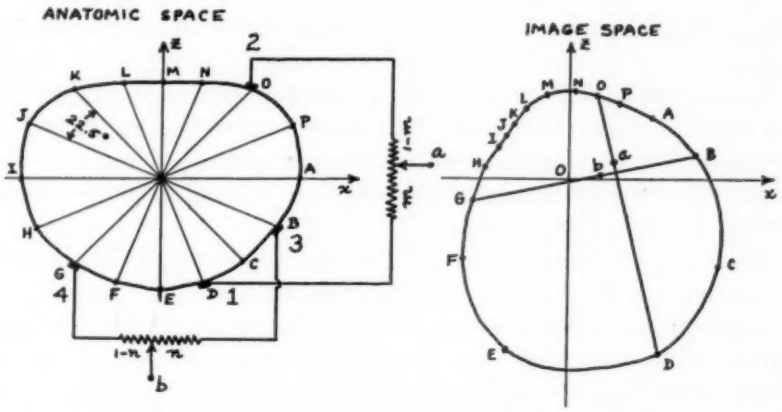

Fig. 4.—Four-electrode cancellation system is shown at the left with electrodes affixed at the transverse level of the heart center. Electrodes 1 and 2, located at D and O, respectively, and potentiometer tap *a* are maintained constant for all cancellations. Electrodes 4 and 3 are moved around the chest for each cancellation. For example, electrode 4 may be fixed at G, and cancellation search is carried out with electrode 3 and potentiometer tap *b*. In the case illustrated, electrode 3 location at B resulted in the best cancellation. On the right the cancellation data are plotted in image space by joining image electrode locations with straight lines and locating points *a* and *b* along these lines as determined by m and n, which were 0.75 and 0.43, respectively, in this example. When this same construction is applied erroneously to anatomic space, it may be seen that points *a* and *b* are very far from coincident

(These limbs are least sensitive of practically all body-surface points to dipole-location effects.) The electrical level of the dipole may be established by temporarily connecting electrode 3 to the right arm and electrode 4 to the left leg with $n = 0.40$. An initial estimate of the level of the ventricles may be made from chest x-ray photographs of the subject. Electrodes 1 and 2 are affixed at this estimated level at roughly opposite points on the chest (as in Fig. 4) for the first trial. If cancellation is not obtained by varying m and the *angular* location of electrode 2, electrodes 1 and 2 should both be raised (or lowered) by equal amounts for another trial, continuing until the best cancellation is obtained with electrodes 1 and 2 at the same anatomic level. Electrodes 1 and 2 are then fixed at this level for the entire remainder of the heart-center determination. (Amplitude equalization of the mirror patterns may be accomplished by connecting an appropriately adjusted resistor from *b* to precordial electrode 1, during these preliminary measurements.)

With electrodes 1 and 2 fixed and with m set to a fixed value, electrode 4 is placed at various locations between anatomic angles A through I at the same anatomic level as electrodes 1 and 2. A search for cancellation with electrode 3 and potentiometer tap *b* is carried out for each location of electrode 4. As few as three cancellations will in some cases lead to a conclusive result, and no more than seven cancellations should ever be required.

Cancellation data may be portrayed in image space as shown in Fig. 4. It has been proved elsewhere[6] that in image space the potentiometer tap lies along a straight line joining the two image points corresponding to the two anatomic points which the potentiometer joins. Hence, tap *a* in Fig. 4 is shown on the straight line joining image points D and O and is located in the ratio m:1 from image point D. Similarly, tap *b* is shown on the straight line joining image points B and G and is located in the ratio n:1 from image point B. Ideally, the two image points *a* and *b* should coincide exactly for all cancellations. However, there are many factors which prevent this such as imperfect heart-dipole behavior, human body inhomogeneities, difference in dipole location between the human heart and the torso model, slight differences in torso shape, mobility of the human dipole, and auricular repolarization effects. Therefore, it is to be expected that the image points *a* and *b* will form at best a small cluster rather than all falling on top of one another.

The remaining two coordinates of the equivalent dipole in the transverse plane may be determined directly from the cancellation data (electrode locations and potentiometer settings) by geometric construction. Transverse image loop data obtained on a torso model for 71 different dipole locations, which should include most subjects, are presented in Appendix I. Cancellation data may be laid out on these loops following the construction scheme of Fig. 4. The image loop which results in least scatter of image points *a* and *b* reveals the dipole location for which the torso model potentials at the transverse level of the heart fit most closely those of the human subject.

RESULTS

Detailed results for one normal male subject will be presented. In this case, the subject was the same individual on whom the torso model was moulded although, as mentioned previously, this is not necessary to obtain reasonable accuracy.

Eleven cancellation experiments for the QRS complex were carried out on this subject at the critical transverse level using No. 27 hypodermic needle electrodes. The heart center was established after four cancellations, but seven additional cancellations were carried out for consistency checks and to make certain that precordial potentials were essentially dipolar. Cancellation coefficients between 2 and 8 per cent, averaging 5 per cent were obtained. All of these results involved one precordial electrode and some of them utilized two precordial electrodes. These data in themselves reveal that precordial potentials may be attributed to an equivalent dipole for the QRS complex to an accuracy of approximately 95 per cent for the individual tested. The cancellation data are shown geometrically in Fig. 5 for five different torso-model image

Fig. 5.—Data-fitting procedure for heart-center determination is illustrated by image loops at the transverse heart level for four dipole locations differing by 1 cm. anatomically from optimum dipole location 13. The same cancellation data for eleven experiments are plotted on each image loop in accordance with the construction procedure in Fig. 4. Twelve points corresponding to the potentiometer settings in image space are enclosed in each case by a circle of the smallest radius which contains all points. It may be seen that the circle for location 13 is the smallest, 3 2 units in diameter. The other circles have diameters of 40, 44, 48, and 44 units for dipole locations 03, 23, 12, and 14, respectively. It is not necessary for the circles to enclose the dipole mid-potential point 0. All image loops have been normalized to have maximum z-axis limits of 280 units using the normalization factors listed in Appendix I. Careful study of the differences among these diagrams reveals the strong influence of dipole location on the transverse image loop.

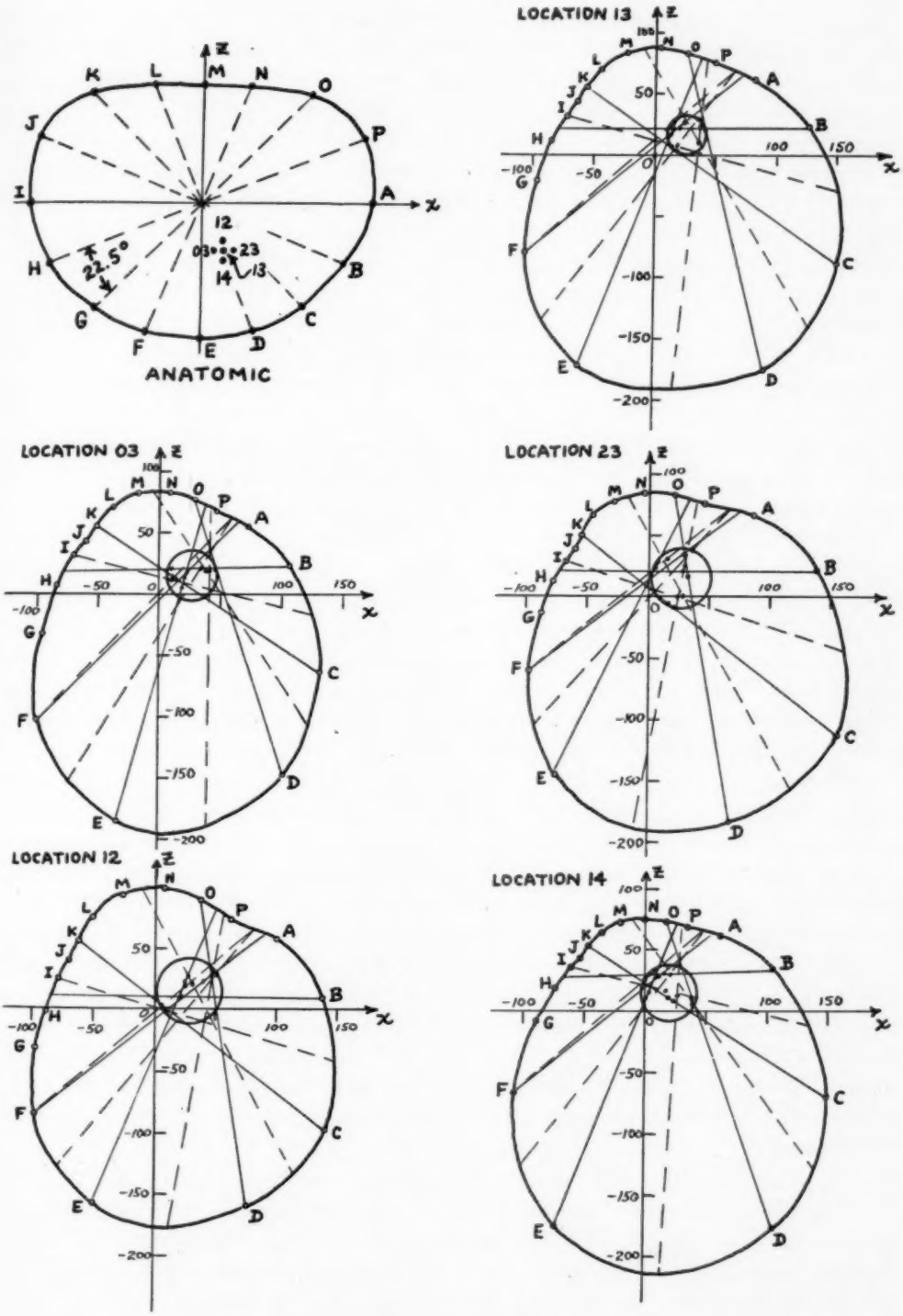

Fig. 5. *(For legend see opposite page.)*

loops corresponding to anatomic dipole locations spaced 1 cm. apart (Appendix I). It may be seen that the cluster of image points *a* and *b* is quite sensitive to dipole location, being a minimum at dipole location 13, since changes in dipole location in the transverse plane of only 1 cm. in either direction along the x or z axes produce significant increases in the diameters of circles which enclose all of the image points. It may be estimated from Fig. 5 that the anatomic location of the dipole in the transverse plane, in this case, is accurate to within approximately ± 0.5 cm. It is interesting to note that location 13 departed by only 1.5 cm. from the initial estimate made from x-ray photographs of the subject's chest, but it has not been established that such correlations would generally be found.

Heart-center determination is a three-dimensional problem that may be simplified by obtaining the y-coordinate separately as described. It should be emphasized, however, that the problem is not assumed to be two-dimensional in the transverse plane. Torso image loops were obtained experimentally in a three-dimensional conducting medium and, in fact, the electrode locations for cancellations are not all precisely at the same level but are distributed between reasonable limits (approximately ± 1 inch anatomically) above and below this level, owing in part to inhomogeneity effects. While cancellation data may be plotted in two dimensions as shown in Fig. 5 without serious error, a three-dimensional analysis is desirable to make certain that the cluster of points *a* and *b* along the y-direction is not excessive. When the eleven cancellation results were analyzed in frontal and sagittal view, it was found that the data cluster for the best fit in the y-direction was comparable to that in the transverse plane, and also that dipole location 13 again yielded minimum scatter.

It is important to recognize that the data do *not* center about the dipole mid-point 0 which, as pointed out previously, neither impairs the quality of the cancellation[6] nor interferes with the data-fitting procedure. Deviation from 0 results from the initial choices of electrode 1 and 2 locations and tap *a* setting which are made before the heart-center location is known. However, having determined the most appropriate image loop it is then possible to construct a terminal whose potential is very nearly at the heart center, to an accuracy within the range of the data scatter. In Fig. 5, for example, electrodes located at the critical transverse level about one-half way between G and H and about one-fourth the way from B toward C joined by a potentiometer set to approximately 0.6 are one of many two-resistor terminals that may be employed to establish the dipole mid-potential external to the human subject for this particular individual.

It is also possible to determine directly the front-to-back (p_z) and right-to-left (p_x) dipole components of the subject in both shape and relative amplitude. For example, p_x may be recorded directly using a bipolar lead connected to the aforementioned terminal electrodes. Its relative standardization factor is obtainable from the length of the line joining the two corresponding points on the image loop. Dipole components for the subject tested are given in Fig. 6 in absolute units. With these components known, it becomes possible to estimate the electrical error of the two-resistor terminal, as follows. The boundary

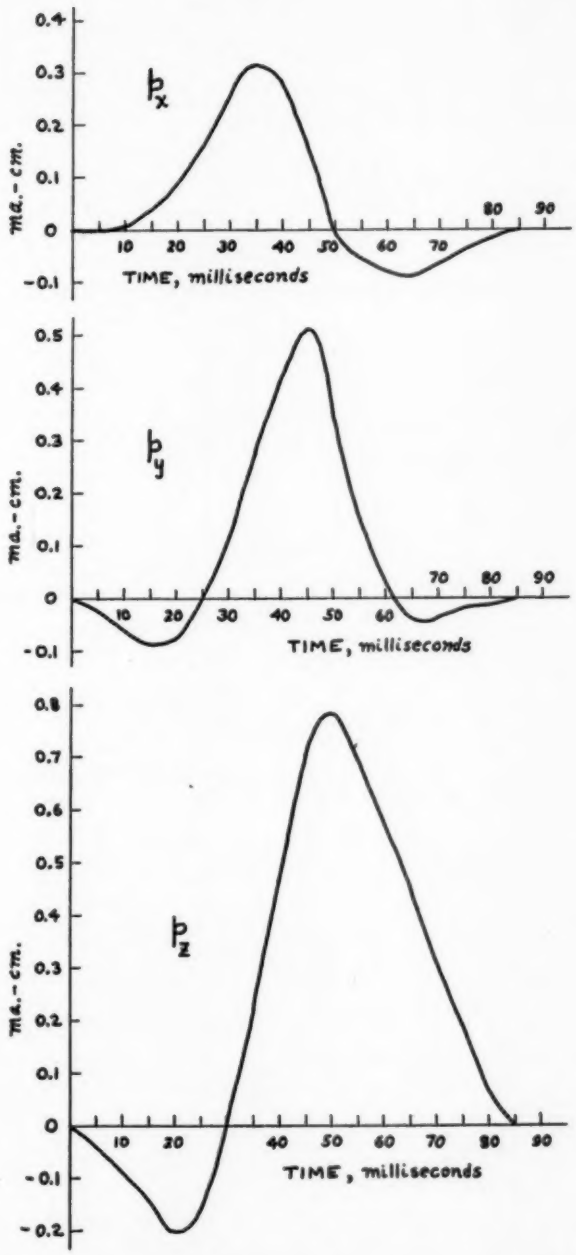

Fig. 6.—Accurate heart-dipole components for the QRS complex of a normal male subject. Transverse components p_x and p_z may be determined from measurements at the transverse level of the heart. The head-to-foot component (p_y) was determined from V_F. Dipole components are given in absolute units (ma.-cm.) based upon the assumption that the resistivity of the human body has an average value of 1,000 ohm-cm.[18] at heart frequencies. These dipole components are useful in the present discussion to estimate the accuracy in millivolts of the heart-center determination, to compute the Wilson central-terminal potential for comparison with its directly measured record, and to compute chest potentials for comparison with true unipolar records.

potential in millivolts around the chest is given approximately by Eq. (2) using absolute units for c_x and c_z which are numerically equal to the relative scale units, shown in Fig. 5 for dipole location 13, divided by 55. It follows that the minimum circle diameter of 32 units in Fig. 5 corresponds to about 0.4 mv., peak, of heart signal; therefore, the terminal may be expected to be accurate to within ± 0.2 mv. (limit of error) which is superior to what may be expected from the Wilson central-terminal in most subjects.

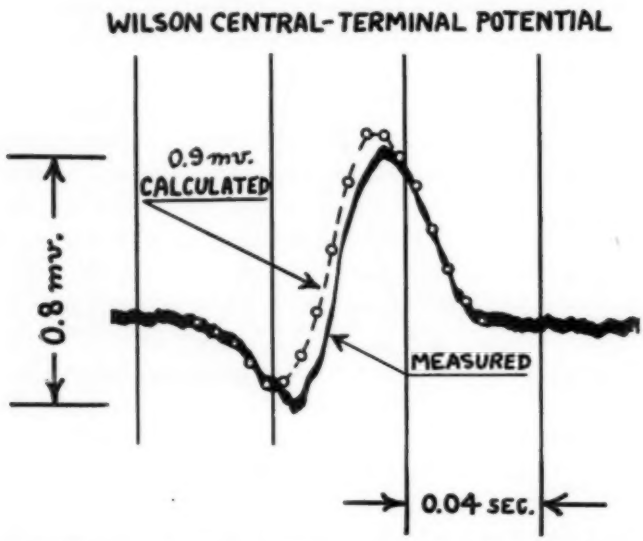

Fig. 7.—Potential difference between the Wilson central-terminal (using 100,000 ohm resistors) and a more accurate two-resistor terminal during the QRS complex is shown recorded at much higher paper speed and amplification than those used in standard electrocardiography. The calculated amplitude, based on experimental measurements on a homogeneous torso model of the male subject containing a dipole at location 13, was 0.88 mv. which is approximately 0.1 mv. greater than the measured peak-to-peak amplitude of 0.79 mv. (Both calculations and measurements must be rounded off to the nearest 0.1 millivolt because of experimental errors). The calculated wave form has been adjusted to have the same peak-to-peak size as the record to compare waveshapes.

The Wilson central-terminal potential may be measured directly with respect to the more accurate two-resistor terminal described previously. In the case of this subject the peak-to-peak amplitude of the Wilson central-terminal potential was 0.79 mv. which is considerably larger than the maximum uncertainity of ± 0.2 mv. of the more accurate reference potential. Results calculated from homogeneous torso model coefficients show close agreement with the human record in both shape and amplitude as may be seen in Fig. 7. It is, of course, necessary to know the head-to-foot dipole component (p_y) to calculate the Wilson central-terminal potential (as well as the limb-lead coefficients) and this may be determined from V_F with sufficient accuracy using a relative coefficient of 115 times the appropriate normalization factor given in Table I.

Finally, an over-all appraisal of the reliability of the entire result of heart-center determination and an assessment of the total conglomerate errors resulting from the various approximations in the method may be carried out by recording true unipolar potentials around the transverse level of the dipole with respect

to the more accurate two-resistor central terminal previously described. These records may be compared with wave forms calculated from torso model coefficients with the dipole location as determined from transverse level cancellations, and using the time varying dipole components of Fig. 6. An illustration of this over-all test is given in Fig. 8 which was carried out at transverse level T_2, 1 inch below the level at which cancellations were obtained. (It was therefore necessary

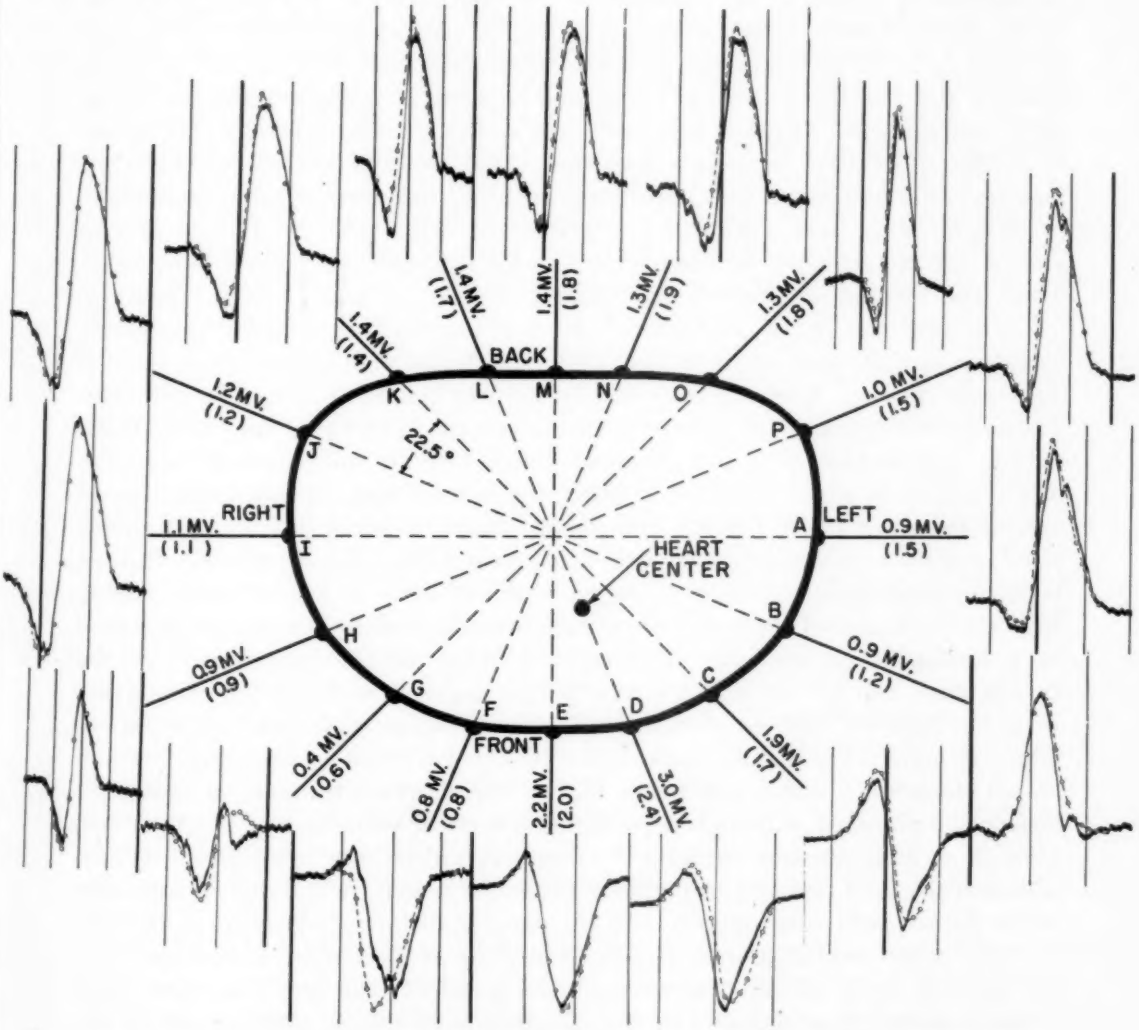

Fig. 8.—Records of unipolar chest potentials during the QRS complex measured with respect to an accurate two-resistor terminal are shown for sixteen points (A through P) around the chest at level T_2 (Fig. 1). Calculated points, shown by small circles at 18 instants spaced 0.005 sec. apart during the QRS complex, are based upon homogeneous torso model coefficients determined for dipole location 13 using the dipole components given in Fig. 6. Each record was made simultaneously with Lead II (not shown) in order to establish the time origin. Measured amplitudes in millivolts are indicated on the radial lines along with the corresponding calculated amplitude in parenthesis. For shape comparison, the calculated wave forms are made equal in peak-to-peak value to the corresponding record. These results represent a sample of a comprehensive study of human body potentials over the entire torso surface[16] in which it was found for the QRS complex that measured and calculated amplitudes agreed within ± 10 per cent for one-half of 190 measurements, and within ± 20 per cent for three-fourths of the measurements. The calculated shapes also agreed well with measured shapes; 82 per cent of the 190 cases were similar to or better than those shown for transverse level points A, B, and C.

to include p_y since c_y is no longer negligible at this level.) Measured and calculated wave forms are compared around the entire chest, including the precordium, and constitute a composite summary of the over-all results.

DISCUSSION

Approximate methods are limited in value unless there is available a means for estimating errors to be expected in the final results. Accuracy estimates of the determination of the electrical center of ventricular depolarization may be made in terms of the measured cancellation coefficients, the scatter of image points *a* and *b* in the transverse plane, and in terms of measured and calculated QRS complex wave forms around the chest at the transverse level of the heart. It is also informative to inquire into the various sources of error so that they may be either minimized by careful experimental procedures, whenever possible, or recognized as basic limitations. Sources of error may be placed in two groups for convenience in discussion: those traceable to assumptions upon which the method is founded, and those traceable to experimental difficulties.

The very concept of an electrical center of heart activity implies that body-surface potentials may be attributed, with high degree of accuracy, to an equivalent heart dipole. This is a basic requirement of the method, and it will automatically fail if this is not fulfilled. In the process of carrying out the determination, cancellation data are obtained which provide an automatic measure of the degree to which the fixed-location dipole hypothesis is applicable. Since cancellations are never perfect, this means that the small nondipolar content of body-surface potentials contributes some error to the over-all result. Human body inhomogeneities constitute a larger source of error, in typical cases, arising from the treatment of the cancellation data in terms of dipole potentials produced in a homogeneous medium. The reproducibility of the cancellation results entails small, but not negligible, errors (if they are done with care) in comparison with the inherent scatter of data arising from inhomogeneities. In addition, inhomogeneities are mainly responsible for the variation in anatomic level of search electrode 3, above and below that of the equivalent dipole, when cancellations are obtained, although there is some vertical variation around the chest even in a homogeneous medium.[14] These variations are typically $\pm$ 1 inch anatomically and are not too serious since the angles A through P for these levels do not shift substantially and the relative distances of points A through P to the origin are not greatly altered from those at the critical transverse level. An over-all check of the determination in terms of true unipolar chest wave forms provides some measure of the inhomogeneity effects taking place in the human subject. The method could possibly be refined, with some difficulty, by using image loops derived from inhomogeneous models, but fortunately errors traceable to the use of homogeneous data appear to be tolerable. A further source of intrinsic error concerns the individual chest contour of the subject. Errors arising from the difference between the subject's chest contour and that for which the data in Appendix I apply are practically negligible compared with inhomogeneity errors, as suggested by Fig. 3. Moreover, transverse image loops for a female torso model differ by less than 10 per cent from those of the male torso model.

Sources of experimental error are numerous and require careful methods and techniques to obtain sensible results. The total time for cancellation experiments may be as great as 10 hours, and this must be done in blocks of 1 to 2 hours' duration because of fatigue. Hence, reproducibility of experimental conditions for each session poses a problem. Such factors as posture, respiration, and reproducible placement of electrodes must be controlled as accurately as practicable. In the present study a snugly fitting vest[16] with a zippered back (tailored to the subject) with small holes corresponding to angles A through P at the various levels was used to reproduce electrode locations to within approximately ± 0.5 cm. (limit of error). Needle electrodes were used to obtain fine delineation of body-surface points at which cancellations occur. As an example of the influence of respiration, detailed cancellations under conditions of very deep inspiration revealed that dipole location was lowered by 1 inch as compared with that in "normal" respiration. Other sources of error and suitable techniques have been discussed elsewhere, with regard to cancellation measurements.[5,6] Additional experimental errors are encountered in determining the dipole components, in setting up a two-resistor terminal, and in recording the QRS complex wave forms around the chest, when obtaining data to check the over-all result. In considering the difficulty of the measurements and the various assumptions which underlie the method, it is indeed remarkable that such satisfactory results are obtainable.

Since changes in location of the equivalent dipole during the QRS complex would impair the quality of cancellation,[6] it is possible to place an upper limit on the amount of dipole motion from the data given here. Analysis of the image loops in Fig. 5, using dipole components p_x and p_z in conjunction with a typical noncancelling residual voltage of 0.05 mv., leads to the conclusion that the maximum possible dipole motion during the QRS complex for the normal subject tested is less than 0.5 cm., assuming the entire residual is traceable to dipole motion and none traceable to the finite size of the depolarization layer. Hence, the dipole location is seen to be fixed to a degree comparable to the experimental uncertainty in determining its location. This result conflicts with the representation of ventricular depolarization as a double layer moving outward through the myocardium, from which an estimated dipole movement of about 2.5 cm. might be expected, and suggests that this concept may require some revision.

Since this study is devoted entirely to the QRS complex, no evidence is provided concerning the dipolar nature of P or T waves or the location of their electrical centers, presuming that such centers exist. Assuming that P and T waves are describable in terms of dipole potentials, it can be shown[5,6] that the centers of P and T activity are not exactly the same as that of the QRS complex, but the differences remain to be established quantitatively.

Extreme departures between the transverse loops in image space and the transverse loop around the chest in anatomic space, with respect to angles A through P as well as effective electrical distances from the heart center, reveal that large errors would be encountered if the anatomic geometry were used as a basis for analysis of electrical results. Data showing a reasonable cluster in

image space using the straight line construction of Fig. 4 become very widely scattered when this same construction is applied erroneously to anatomic space. This is true for the data cluster shown in Fig. 5, as well as for other clusters not presented here which center on the dipole point 0. Consequently, conclusions based on anatomic considerations may be expected to be seriously in error.

It is hoped that the method of heart-center determination presented here, while approximate in nature and molested by human-body inhomogeneities, will be attempted by other investigators because of the extremely crucial role played by the location of the heart dipole. Quantitative answers to such questions as the range of variation of dipole location among normals and changes in location resulting from heart disease are of basic importance. Moreover, the fundamental question of correlation between anatomic orientation and electrical behavior of the heart cannot be resolved until proper account is taken of the location of the heart center.

SUMMARY

The most influential parameter in the human heart-body electrical system is the location of the electrical center of the heart. A new research method for locating the electrical center of the QRS complex may be carried out using a precision cancellation technique which fits potentials around the chest of a human subject at the transverse level of the heart to dipole potentials produced in a homogeneous torso model. The method fails automatically if the dipole representation is invalid. The electrical center of the QRS complex may be established by this technique to an accuracy of ± 0.5 cm. anatomically and ± 0.2 mv. electrically. Once the center is determined, dipole components during the QRS complex may be measured accurately. Dipole movement during the QRS complex in a normal male subject is shown to be less than 0.5 cm. For the QRS complex in a normal male subject it is shown that precordial potentials are 95 per cent dipolar. An accurate reference terminal may be deduced from experimental data and enables direct measurement of the Wilson central-terminal potential on the intact human subject, which is not negligible. Amplitude and shape of body potentials may be predicted with good accuracy from dipole coefficients of a homogeneous torso model. Since the method is insensitive to individual chest contour, detailed torso data are given which may be applied to a wide variety of subjects.

SUMMARIO IN INTERLINGUA

Le plus significative parametro in le systema electric corde-corpore, i.e. le electric centro del corde, pote esser locate pro depolarisation ventricular intra ±0,5 cm anatomicamente e intra ±0,2 mv electricamente per medio de un technica de precision de cancellation que permitte le coordination de potentiales circa le thorace del subjecto con potentiales dipolar de un homogenee torso modello. In re le complexo QRS de un masculo normal le sequente constatationes es presentate: componentes dipolar pote esser determinate accuratemente; un accurate termino central pote esser construite; le potentiales precordial es

dipolar a 95 pro cento; le potential del termino central Wilson differe significativemente ab le potential del centro cardiac; le potentiales precordial e le potentiales del termino central Wilson pote esser predicite satis accuratemente—tanto in forma como etiam in amplitude—ab resultatos del homogenee torso modello. Es presentate datos que rende possible le application de iste methodos a un varietate de subjectos.

APPENDIX I. TORSO MODEL TRANSVERSE IMAGE LOOPS

The method of heart-center determination involves fitting data obtained at the transverse level of the ventricles around the chest of a human subject with those obtained at the same level in a homogeneous torso model with known dipole location. It is unnecessary to compare specific wave shapes; instead, cancellation data in terms of electrode locations and potentiometer settings may be used. The procedure involves plotting human cancellation data on various transverse loops in image space of the torso model, selecting by this process that loop (and corresponding dipole location) for which the data cluster shows minimum scatter.

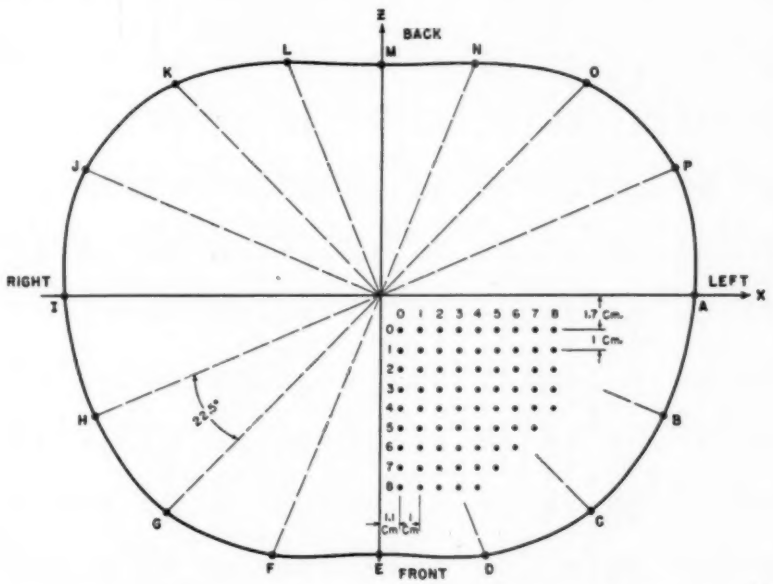

Fig. 9.—Transverse anatomic section of male torso model showing 71 different dipole locations used to determine transverse image loops. Dipole locations are specified by a two-digit number the first of which gives the x-axis location number and the second of which gives the z-axis location number. Thus, dipole location 34 is in the third column (on the x-axis) and in the fourth row (on the z-axis). Dipole location 13 was, in the instance reported, the one which resulted in the best fit of torso and human data. Location 22 was estimated initially as the ventricle center from x-ray films. The x-axis passes through both mid-axillary lines; the z-axis through front and back anatomic midlines. Anatomic distance from A to I is 33 cm., and from E to M is 25 cm.

Transverse image loops were determined experimentally for 71 different dipole locations, illustrated in Fig. 9, which should cover the range of heart centers expected in most subjects. Image loop data are presented in Table I. If the physical dimensions of the subject under test do not agree with those in Fig. 9 the entire scale of the drawing may be adjusted. For example, if the subject's dimensions are, say, 20 per cent smaller than those shown but approximately in the same proportions, then the dipole locations and separations may all be reduced correspondingly by 20 per cent.

TABLE I

DIPOLE LOCATION		00	01	02	03	04	05	06	07	08	10	11	12	13	14	15	16	17	18	20	21	22	23	24
NORM. FACTOR		1.18	1.16	1.08	0.94	0.76	0.62	0.45	0.32	0.20	1.21	1.20	1.12	1.00	0.85	0.69	0.51	0.35	0.24	1.19	1.20	1.12	0.98	0.84
A	c_x	110	103	91	73	54	39	25	15	7	127	115	98	82	62	45	28	16	7	138	126	106	85	64
	c_z	34	45	52	55	52	51	44	40	35	41	52	57	62	61	60	52	44	41	47	56	65	67	67
B	c_x	127	129	122	106	85	67	45	30	17	144	148	136	126	104	83	56	34	20	157	162	158	137	115
	c_z	−18	−2	11	24	31	38	38	38	34	−25	−11	7	23	35	43	44	41	40	−33	−17	2	22	37
C	c_x	106	123	132	132	122	111	89	67	44	112	130	139	150	149	141	114	84	60	110	128	147	155	162
	c_z	−90	−87	−79	−63	−43	−23	−2	13	22	−108	−108	−99	−89	−69	−46	−18	5	21	−126	−128	−126	−112	−94
D	c_x	64	78	91	102	108	119	117	116	98	57	64	76	92	106	124	128	133	134	40	46	58	67	81
	c_z	−131	−142	−146	−148	−138	−129	−108	−77	−48	−143	−156	−161	−175	−176	−165	−155	−124	−101	−149	−163	−175	−183	−192
E	c_x	−15	−21	−27	−34	−41	−54	−67	−89	−111	−30	−43	−50	−61	−73	−90	−102	−114	−127	−44	−56	−67	−76	−88
	c_z	−144	−162	−177	−185	−182	−187	−179	−161	−143	−140	−151	−158	−172	−175	−167	−158	−140	−120	−132	−138	−145	−145	−147
F	c_x	−70	−84	−93	−100	−98	−99	−89	−75	−57	−79	−92	−97	−106	−106	−104	−91	−73	−57	−81	−91	−98	−98	−99
	c_z	−106	−110	−110	−102	−86	−70	−48	−27	−6	−96	−92	−87	−80	−67	−50	−29	−12	6	−83	−78	−71	−60	−48
G	c_x	−90	−98	−101	−96	−86	−76	−60	−46	−31	−93	−100	−98	−97	−89	−80	−63	−47	−34	−90	−94	−95	−89	−82
	c_z	−61	−55	−45	−31	−17	−3	8	17	22	−53	−43	−32	−21	−8	5	14	21	27	−45	−34	−23	−13	−2
H	c_x	−94	−96	−93	−84	−69	−58	−44	−33	−22	−96	−97	−90	−85	−74	−64	−47	−35	−25	−91	−91	−89	−79	−70
	c_z	−25	−15	−4	7	15	23	26	29	29	−21	−10	−1	11	19	27	30	30	33	−17	−6	3	13	20
I	c_x	−91	−88	−81	−70	−56	−45	−34	−24	−16	−92	−88	−80	−72	−61	−51	−38	−27	−20	−88	−84	−79	−68	−60
	c_z	8	19	26	32	33	36	35	35	31	8	18	25	32	36	39	38	34	35	7	17	23	29	35
J	c_x	−85	−80	−71	−60	−47	−38	−28	−20	−14	−87	−82	−72	−64	−53	−43	−32	−23	−17	−84	−79	−73	−61	−53
	c_z	29	37	42	44	43	42	39	37	32	27	35	39	43	43	44	41	37	36	23	30	36	39	41
K	c_x	−80	−72	−63	−51	−40	−31	−23	−17	−11	−85	−76	−64	−56	−46	−37	−28	−20	−15	−83	−76	−67	−56	−47
	c_z	58	60	60	56	51	48	41	38	33	52	55	55	55	53	50	44	39	37	45	49	50	50	49
L	c_x	−65	−56	−48	−38	−29	−23	−17	−13	−9	−73	−62	−52	−44	−36	−29	−21	−16	−12	−76	−66	−57	−47	−39
	c_z	96	91	82	71	61	53	45	40	34	88	84	75	70	64	57	48	41	38	78	74	70	64	60
M	c_x	−26	−23	−21	−17	−14	−11	−10	−8	−6	−39	−44	−27	−24	−20	−17	−13	−11	−9	−49	−42	−36	−29	−25
	c_z	126	111	97	83	68	58	49	42	35	121	108	93	83	72	63	53	43	40	114	102	90	78	69
N	c_x	26	20	14	8	5	1	−1	−2	−3	17	11	7	3	0	−3	−4	−5	−6	2	0	−2	−4	−7
	c_z	122	109	96	83	68	58	49	42	35	128	113	97	87	75	64	54	44	40	131	112	99	85	74
O	c_x	63	51	40	28	19	12	6	2	0	60	49	36	26	17	9	4	0	−2	52	41	35	20	12
	c_z	97	94	86	76	65	57	48	42	35	109	101	89	83	73	64	53	44	40	116	106	95	83	74
P	c_x	85	74	62	47	33	23	13	7	3	91	78	62	49	35	23	13	6	1	91	78	61	45	31
	c_z	67	72	71	68	59	54	47	41	35	79	79	73	75	69	62	52	44	40	90	88	85	77	72

TABLE I—Continued

	c_z	67	72	71	68	59	54	47	41	35	79	79	73	75	69	62	52	44	40	90	88	85	77	72		

TABLE I—Continued

DIPOLE LOCATION		25	26	27	28	30	31	32	33	34	35	36	37	38	40	41	42	43	44	45	46	47	48	50	51
NORM. FACTOR		0.68	0.50	0.34	0.22	1.14	1.12	1.03	0.92	0.80	0.64	0.49	0.37	0.21	1.07	1.04	0.94	0.84	0.70	0.56	0.46	0.34	0.24	0.97	0.91
A	c_x	44	26	14	5	149	133	113	86	64	42	24	11	1	160	141	113	87	58	37	20	6	5	172	145
	c_z	62	54	45	38	55	68	77	78	76	70	62	57	43	63	78	83	84	79	73	66	58	54	73	85
B	c_x	88	59	36	18	177	180	175	156	130	97	66	42	17	193	199	190	171	136	104	70	41	17	207	213
	c_z	46	47	43	38	−46	−24	1	26	45	55	58	57	45	−59	−36	−5	25	47	62	65	62	58	−79	−53
C	c_x	153	129	101	65	105	125	146	165	178	175	161	139	84	92	112	135	161	173	188	188	160	121	72	89
	c_z	−66	−34	−4	17	−141	−149	−150	−143	−127	−97	−60	−16	16	−153	−166	−169	−169	−152	−132	−97	−39	13	−158	−172
D	c_x	95	109	125	135	23	26	33	41	52	62	78	107	137	2	3	6	8	11	14	19	25	49	−16	−19
	c_z	−190	−180	−157	−132	−150	−166	−181	−192	−204	−207	−208	−210	−173	−144	−158	−170	−181	−184	−196	−202	−205	−215	−132	−140
E	c_x	−99	−105	−107	−98	−55	−65	−75	−85	−95	−101	−106	−111	−88	−62	−72	−78	−87	−89	−95	−96	−92	−88	−67	−73
	c_z	−139	−118	−99	−70	−118	−123	−126	−128	−122	−110	−93	−77	−42	−100	−103	−102	−98	−87	−75	−61	−42	−20	−84	−81
F	c_x	−93	−80	−64	−46	−82	−89	−92	−95	−94	−86	−76	−67	−45	−80	−85	−86	−86	−81	−76	−69	−59	−50	−77	−79
	c_z	−32	−15	−1	12	−71	−65	−58	−47	−34	−20	−5	8	18	−59	−51	−42	−33	−19	−7	5	16	27	−46	−38
G	c_x	−72	−58	−43	−30	−88	−90	−88	−84	−78	−69	−57	−49	−31	−82	−83	−81	−77	−69	−63	−55	−46	−40	−78	−77
	c_z	10	18	23	26	−37	−27	−18	−7	4	13	22	29	29	−30	−20	−10	−2	8	17	25	30	37	−23	−14
H	c_x	−59	−46	−34	−24	−88	−85	−82	−75	−68	−57	−47	−40	−26	−82	−81	−75	−71	−61	−54	−48	−39	−35	−77	−75
	c_z	26	30	30	30	−14	−4	5	14	21	27	32	36	32	−11	−2	7	15	21	28	33	36	41	−9	0
I	c_x	−49	−38	−28	−19	−84	−81	−74	−67	−60	−50	−41	−34	−23	−80	−77	−70	−64	−55	−48	−42	−35	−31	−75	−71
	c_z	37	37	34	32	6	15	22	29	33	36	38	40	34	5	14	21	27	31	35	38	39	43	4	13
J	c_x	−43	−33	−25	−18	−82	−76	−69	−62	−55	−45	−37	−31	−21	−78	−74	−67	−61	−51	−45	−39	−33	−30	−74	−69
	c_z	41	40	37	33	19	26	32	37	40	41	41	43	36	16	23	28	34	36	39	41	41	44	14	20
K	c_x	−39	−29	−22	−16	−81	−74	−66	−58	−50	−41	−34	−29	−19	−78	−72	−64	−57	−49	−43	−37	−31	−28	−74	−68
	c_z	47	43	38	34	38	43	45	46	47	46	45	45	36	31	36	40	41	42	43	44	43	45	25	31
L	c_x	−32	−24	−18	−14	−79	−67	−59	−51	−43	−36	−29	−26	−18	−77	−69	−59	−51	−43	−38	−33	−29	−27	−74	−66
	c_z	53	47	40	35	66	65	63	60	57	53	49	47	38	57	56	55	54	50	49	48	45	46	45	46
M	c_x	−22	−17	−14	−11	−58	−49	−42	−37	−32	−27	−23	−21	−15	−63	−55	−46	−41	−35	−31	−27	−25	−24	−66	−57
	c_z	60	51	42	36	103	94	84	75	68	59	53	50	39	91	83	75	68	60	55	52	48	48	76	70
N	c_x	−8	−8	−8	−8	−10	−11	−12	−14	−14	−15	−15	−15	−12	−24	−23	−22	−21	−20	−20	−20	−20	−21	−36	−32
	c_z	63	53	44	37	128	111	96	85	75	64	56	52	40	120	103	90	79	67	61	56	50	49	107	92
O	c_x	5	0	−3	−5	42	30	20	11	4	−2	−6	−9	−9	29	18	9	2	3	−9	−12	−14	−18	14	5
	c_z	64	54	44	37	124	111	98	87	76	67	58	53	41	125	111	96	85	72	64	59	52	50	121	105
P	c_x	19	10	3	−1	91	74	56	40	25	13	4	−2	−6	87	67	47	31	17	7	−1	−7	−13	78	56
	c_z	63	54	44	38	100	99	93	85	76	68	60	55	42	108	105	95	86	75	67	61	54	51	116	105

TABLE I—Continued

DIPOLE LOCATION		52	53	54	55	56	57	60	61	62	63	64	65	66	70	71	72	73	74	75	80	81	82	83	84
NORM. FACTOR		0.82	0.70	0.58	0.45	0.35	0.25	0.84	0.80	0.70	0.59	0.48	0.37	0.28	0.66	0.64	0.56	0.48	0.40	0.30	0.51	0.48	0.43	0.38	0.32
A	c_x	112	80	51	28	12	−2	175	143	108	71	41	18	3	168	139	98	61	31	8	165	121	80	43	14
	c_z	92	87	79	68	59	51	92	101	100	93	82	68	56	91	108	106	97	83	66	100	116	111	100	85
B	c_x	204	176	139	99	64	31	214	226	220	189	146	99	59	206	239	232	206	162	101	201	234	243	222	167
	c_z	−13	25	50	63	65	58	−102	−74	−25	25	60	73	69	−124	−99	−41	25	75	83	−128	−134	−72	27	101
C	c_x	113	139	161	178	186	167	47	61	81	107	138	169	201	17	26	42	66	97	137	−8	−5	3	14	36
	c_z	−179	−181	−175	−159	−122	−70	−153	−170	−180	−188	−195	−190	−163	−131	−148	−160	−178	−193	−187	−103	−117	−132	−152	−164
D	c_x	−20	−20	−22	−26	−33	−50	−32	−37	−39	−42	−46	−51	−59	−42	−48	−50	−55	−60	−63	−47	−53	−56	−64	−69
	c_z	−147	−151	−153	−152	−157	−152	−110	−119	−123	−123	−120	−114	−112	−86	−90	−91	−91	−89	−80	−64	−62	−62	−60	−54
E	c_x	−77	−80	−80	−78	−75	−70	−67	−72	−75	−73	−71	−67	−62	−62	−68	−68	−68	−67	−61	−59	−61	−63	−67	−65
	c_z	−76	−69	−58	−44	−33	−16	−67	−62	−56	−46	−36	−23	−13	−47	−43	−35	−28	−19	−10	−33	−26	−20	−13	−4
F	c_x	−79	−76	−70	−62	−56	−48	−72	−74	−72	−68	−62	−55	−49	−64	−68	−65	−62	−59	−52	−60	−60	−59	−61	−59
	c_z	−30	−19	−9	−2	9	18	−35	−27	−18	−10	−2	8	14	−24	−17	−9	−1	6	11	−16	−9	−2	6	13
G	c_x	−74	−67	−61	−52	−47	−39	−72	−71	−68	−62	−55	−49	−42	−63	−66	−62	−58	−54	−48	−59	−58	−57	−58	−55
	c_z	−5	4	11	18	23	27	−18	−8	−1	7	14	19	23	−11	−4	3	10	17	19	−7	0	7	14	20
H	c_x	−70	−63	−55	−48	−42	−35	−71	−69	−64	−58	−52	−45	−39	−63	−62	−59	−56	−52	−45	−58	−57	−56	−56	−54
	c_z	8	15	21	25	28	31	−6	2	10	15	21	25	27	−3	4	11	16	22	23	−1	6	12	18	24
I	c_x	−66	−58	−51	−43	−38	−33	−70	−67	−61	−55	−48	−42	−37	−61	−61	−57	−53	−49	−43	−57	−56	−54	−54	−52
	c_z	20	24	28	30	32	33	4	12	18	23	26	29	30	3	11	16	21	26	26	4	10	16	22	26
J	c_x	−63	−55	−48	−41	−36	−31	−69	−66	−60	−53	−46	−40	−35	−61	−60	−55	−52	−48	−42	−56	−55	−53	−53	−51
	c_z	25	29	32	33	34	35	11	18	23	27	29	31	31	9	15	20	24	28	28	8	13	18	24	28
K	c_x	−62	−53	−46	−39	−34	−30	−69	−65	−58	−52	−45	−39	−35	−61	−60	−54	−51	−47	−41	−57	−55	−53	−53	−50
	c_z	34	36	36	36	36	36	20	26	29	32	33	33	33	15	21	25	28	31	30	12	17	21	27	30
L	c_x	−59	−50	−43	−36	−32	−28	−69	−64	−57	−49	−43	−37	−33	−61	−59	−53	−49	−46	−39	−57	−55	−52	−51	−49
	c_z	47	44	43	40	39	38	36	39	39	39	38	37	35	26	31	32	34	35	33	20	24	27	31	33
M	c_x	−49	−42	−36	−31	−28	−26	−65	−59	−51	−45	−38	−33	−31	−60	−56	−50	−45	−42	−37	−57	−53	−50	−49	−47
	c_z	64	57	51	46	43	40	61	59	54	49	45	42	38	45	45	44	42	42	36	33	34	35	37	38
N	c_x	−30	−27	−25	−23	−23	−23	−43	−39	−36	−32	−30	−28	−26	−46	−44	−40	−37	−36	−33	−48	−45	−43	−44	−43
	c_z	80	69	60	51	46	42	91	81	70	61	54	47	41	69	65	58	52	48	41	53	49	47	45	44
O	c_x	−2	−7	−11	−14	−16	−18	−2	−8	−13	−16	−18	−20	−21	−15	−20	−22	−25	−27	−27	−27	−29	−31	−34	−37
	c_z	90	77	66	55	49	44	110	98	83	70	60	51	44	91	82	70	62	55	45	75	66	59	55	50
P	c_x	38	21	9	−1	−7	−13	65	43	25	10	−1	−9	−14	45	27	10	−1	−11	−17	25	7	−6	−17	−25
	c_z	95	83	70	59	52	47	117	108	93	79	67	57	48	108	99	85	73	64	52	99	87	76	68	60

These model data were obtained using a unipolar reference potential technique in conjunction with a finite dipole.[17] With such a dipole oriented exactly along the y-axis of Fig. 1, its location along the y-axis was determined such that the potential around the transverse level at which measurements were to be performed was negligible in comparison with potentials produced for x or z-axis dipole orientations. This condition prevailed over the entire range of eccentricities employed. Moreover, the anatomic location on the y-axis of the dipole was found to be essentially in the plane of the critical transverse level. The dipole was then oriented, at this level, along the x and z axes, respectively, and the transverse level boundary potentials were measured with respect to the dipole mid-potential. These potentials are approximately proportional to c_x and c_z, respectively, as indicated by Eq. (2). Each determination was repeated with reversed dipole orientation in order to minimize small errors traceable to the presence of the insulating rod supporting the dipole within the medium. The data are accurate to approximately 5 per cent. Additional tests were performed at levels where the chest contour was somewhat different, but the coefficients in the transverse plane of the dipole had substantially the same relative values for the same dipole eccentricity, as expected from the previously mentioned property of insensitiveness to detailed chest contour.

Potentials at the transverse level become larger as the dipole location becomes more eccentric. Consequently, coefficients c_x and c_z yield transverse image loops whose size increases with increased eccentricity. Since the data-fitting procedure does not depend upon the absolute size of the image loops, but only upon the image locations of the electrodes and the ratios of the potentiometers, all of the image loops have been adjusted to be about the same size. This was accomplished by multiplying the torso model data by the normalization factors given in Table I for each dipole location, and yields image loops measuring a total length along the z axis of 280 units. It is informative, however, to plot c_x and c_z as measured without normalization to appreciate the marked influence of eccentricity on amplitude of the boundary potential.

Coefficients listed in Table I for a normalization factor of 1.0 are ten times the unipolar potential in millivolts measured on the torso model. Thus, for dipole location 13 (normalization factor = 1.0) a value of 100 units corresponds to 10 millivolts. When the normalization factor is not unity, torso millivolts may be obtained by reconverting the data in Table I. For example, in dipole location 08 the normalization factor is 0.2; hence, a listed unit of 100 corresponds to a measured potential of 10/0.2 = 50 millivolts. By assuming the body has an average resistivity of 1000 ohm-cm.,[18] the coefficients listed in Table I may be converted to absolute units, first by removal of the normalization and then dividing by 55, as indicated in the following formula:

$$c_{abs} = \frac{c_t}{55 \times (\text{normalization factor})} \qquad (4)$$

where c_t is the tabular value of c_x or c_z, and c_{abs} is the absolute coefficient in mv./ma.-cm. When c_{abs} is multiplied by a dipole component expressed in ma.-cm., as in Fig. 6, the product yields millivolts on the human subject.

Active participation and interest shown by Dr. Calvin F. Kay, who served as the subject for the results presented, are gratefully acknowledged. Assistance was provided in the execution of the experiments by Dr. George Seiden and Dr. Robert A. Keisman. Dr. L. G. Thomson helped with the analysis.

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THE ELECTROCARDIOGRAM OF ACUTE PORPHYRIA

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ACUTE porphyria has been among the various conditions associated with changes of the electrocardiogram. Eliaser and Kondo[1] reported slurring of the S-T segment as a characteristic of the electrocardiogram in their report on one case. Hegglin[2] found a relative prolongation of the Q-T interval. During the past six years, eighteen patients with disorder of porphyrin metabolism have been studied at the University of Texas Medical Branch Hospitals. In these eighteen cases of porphyria, electrocardiograms were made in ten patients and eight of the latter had electrocardiograms taken while in acute porphyrian crisis. The paucity of literature in reference to the ECG in this disorder and the inability to demonstrate the findings listed by previous writers prompted this report of negative electrocardiographic findings.

Each of the ten patients presented the classical clinical picture of acute porphyria of psychic instability, abnormal neurologic findings, recurrent severe abdominal pain accompanied by findings of ileus, leukocytosis, and the demonstration of abnormal porphyrins in the urine. Of the ten patients, eight were considered to have primary porphyria, and in the other two the acute porphyria was considered secondary to barbiturates in one and secondary to chronic lead poisoning in the other.

TABLE I

CASE	AGE	SEX	RACE*	CARDIAC RATE	BP (ACUTE)	BP (CONVL.)	ASSOC. FINDINGS
1.	39	F	W	104	180/110	110/70	
2.	22	M	W	136	150/110	130/80	Exp. (autopsy)
3.	29	F	N	54	150/80	140/80	I.V. septal defect
4.	40	M	W	116	170/110	126/90	
5.	44	F	W	124	160/104	90/60	Secondary to barb.
6.	43	M	W	122	180/80	110/80	
7.	34	F	W	118	150/112	122/70	
8.	35	F	N	140	180/120	130/90	
9.	42	M	W	75	?	104/60	Not seen as acute
10.	60	M	W	63	?	140/90	Not seen as acute Secondary to lead

*W = white; N = Negro.

The race, sex, and age distribution of the patients are noted in Table I. The characteristic elevation of the blood pressure to hypertensive levels and the tachycardia commonly associated with this disorder are noted. The one patient

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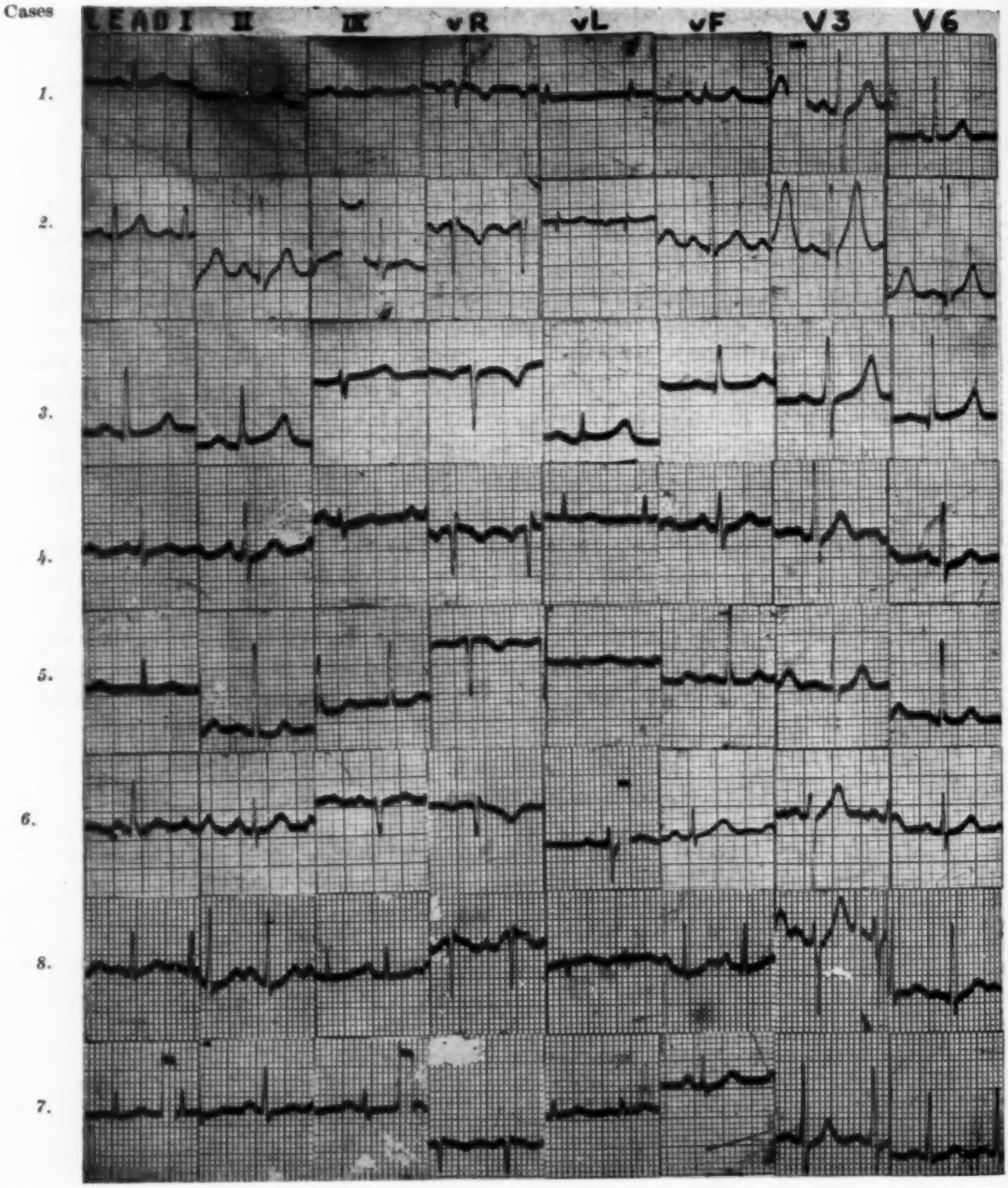

Fig. 1.—Acute porphyria.

with electrocardiograms taken during an acute crisis who did not show the hypertension or tachycardia had an associated congenital intraventricular septal defect. This patient was the only one to have any symptomatology or clinical findings of cardiovascular disease. Patients nine and ten were not seen in an acute stage of the illness.

The electrocardiograms of the patients when acute (Fig. 1) and when convalescent demonstrated normal P-R, QRS, and Q-T intervals. A low QRS voltage was present in one patient, and this remained after the acute illness had subsided. The relative prolongation of the Q-T interval as reported by Hegglin was not encountered in any of our patients. The elevation of the S-T segment of Lead I and the slurring of the S-T segment of Lead III as reported in the one case of Eliaser and Kondo were not present in any of our cases. No abnormality of the P wave, QRS complex, T or U wave was present.

DISCUSSION

An important pathologic process of acute porphyria is considered to be the angiospasm which could affect the coronary circulation and produce evidences of ischemia and injury. None of our patients demonstrated electrocardiographic evidence of an embarrassed myocardial circulation. At autopsy the heart of the one patient who expired, Case 2, did not show gross or microscopic pathology. The cause of death in this patient was respiratory paralysis.

SUMMARY

The literature contains two reports in which abnormalities of the electrocardiograms have been attributed to acute porphyria. The electrocardiograms of our eight patients with acute porphyria were normal except for the presence of sinus tachycardia.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

Le litteratura medical contine reportos isolate de casos in que anormalitates del electrocardiogramma esseva attribuite a acute porphyrinuria. Iste anormalitates esseva specificamente le prolongation del intervallo Q-T o cambiamentos in le segmentos S-T. Le electrocardiogrammas del octo patientes de acute prophyrinuria qui es coperite per le presente studio exhibiva nulle tal cambiamentos. Illos esseva normal excepte que illos revelava le presentia de tachycardia sinusal.

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AN OCTAXIAL REFERENCE SYSTEM DERIVED FROM A NONEQUILATERAL TRIANGLE FOR FRONTAL PLANE VECTORCARDIOGRAPHY

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THE weight of evidence indicates that the frontal plane triangle commonly used in electrocardiography is not equilateral from the electrical standpoint.[1-5] This triangle is scalene as illustrated in Fig. 1, *a*. Such a triangle should be more representative of the true situation pertaining to the electrical field of the heart than is the equilateral triangle. It is the purpose of this paper to illustrate the use of this nonequilateral triangle and an octaxial system derived from it for the estimation of the direction and magnitude of mean QRS and T vectors in the frontal plane.

The configuration of the nonequilateral triangle* shown in Fig. 1 is derived from experimental data using accurately formed homogeneous torso models[1,4] with an immersed current dipole. These data are plotted as an image surface[1,4] from which surface potentials may be derived by geometric construction. In this paper only three points on the image surface, the right arm, left arm, and left leg, are utilized. However, the image surface concept is a very useful and illuminating one in electrocardiography and is basic to a proper understanding of vector methods.

DEVELOPMENT OF THE OCTAXIAL REFERENCE SYSTEM

The addition of the unipolar extremity leads to Fig. 1, *a* gives us Fig. 1, *b*. It should be noted that the Wilson Central Terminal corresponds in image space to the median point of the limb lead triangle. This is then rearranged as a hexaxial reference system as illustrated in Fig. 1, *c*. It will be seen at once by inspection of Fig. 1, *c* that disproportionately large angles exist between the axes of Leads aV_L and I and between the axes of I and aV_R. It seems logical therefore to add two additional lead axes, each bisecting the aforementioned large angles. An octaxial reference system with the two new leads is shown in Fig. 1, *d*.

The triangle used in Fig. 1 was derived from the electrical image surface diagram of Frank by projecting the limb-lead triangle onto the frontal plane.

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*The triangle in Fig. 1 was constructed from data of Frank and Kay[6] using a dipole location at the same level as their location 2, Fig. 2, but 1.5 cm. to the left and 0.5 cm. toward the back.

Actually the limb-lead triangle is not parallel to the frontal plane, being tilted backward and toward the right.[4] The projected triangle is similar to the so-called Burger triangles constructed by several other investigators.[1,2,3,5]

Fig. 1 is applicable to an individual male with average build and heart location in a state of "normal" respiration. The use of the same nonequilateral triangle for all subjects as shown in Fig. 1 is probably a source of some degree of error due to variations in heart-dipole location from person to person. The dipole location is of primary and critical importance in determining the electrical

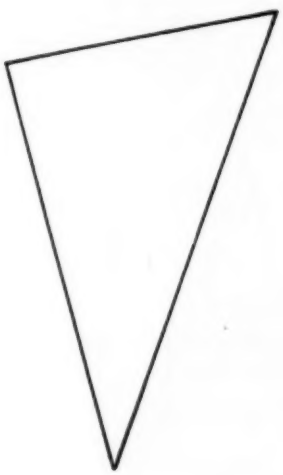

Fig. 1a

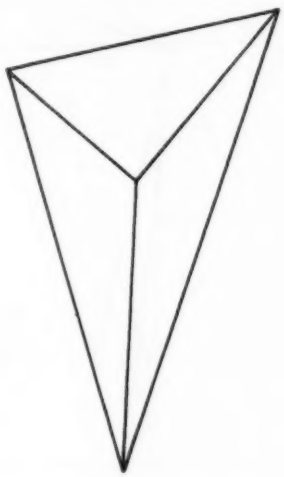

Fig. 1b

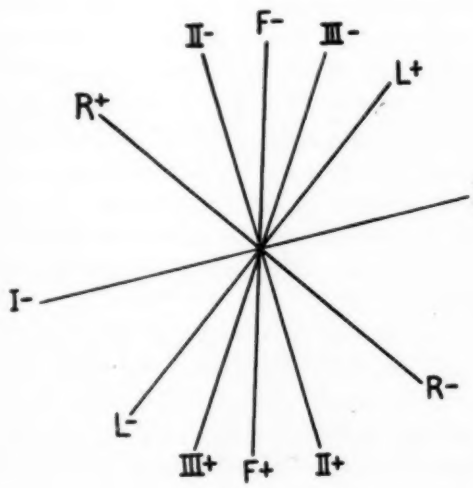

Fig. 1c

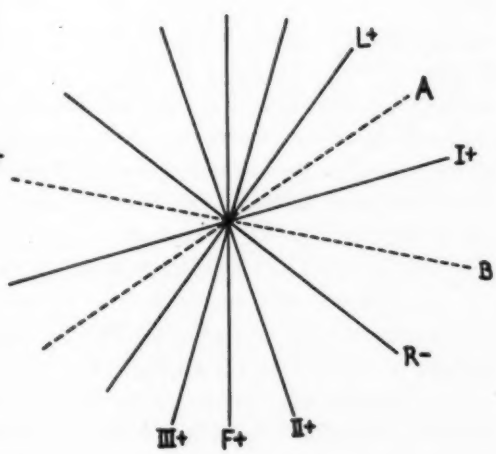

Fig. 1d

Fig. 1.—*a*, Lead vectors for the three standard limb leads in the form of a nonequilateral triangle. *b*, Same as *a* with the addition of the three "unipolar" extremity lead vectors. *c*, This is derived from *b* which is rearranged in the form of a hexaxial reference system. *d*, Represents the octaxial reference system formed by the addition of two synthetic leads "*A*" and "*B*" to *C*.

field of the heart.[6] Even so, it is believed that the use of this average nonequilateral triangle should introduce less error in most individuals than the customary Einthoven triangle. Variations in the frontal-plane projection of the limb-lead triangle produced by changes in dipole location are illustrated in Fig. 2. These projections were constructed from data of Frank and Kay using dipole locations *1, 3, 5, 7* of their Fig. 2.[6]

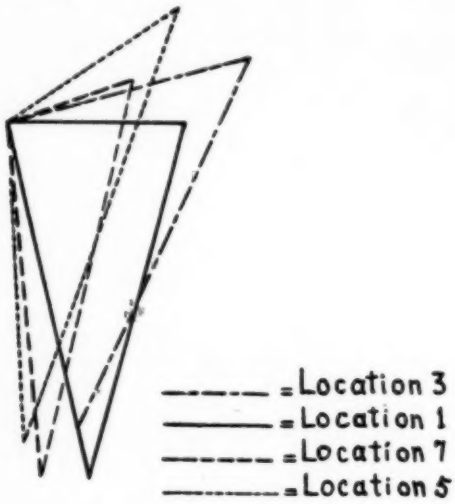

Fig. 2.—Variations in the nonequilateral triangle caused by changes in heart dipole location. Dipole locations are those described,[6] see text.

Brody and Romans[3] have stated: "For exactness in summating the effects of a great number of doublets it would probably be necessary to establish many Burger triangles throughout the cardiac region . . . point A for the electromotive forces arising from the right ventricle; point B for the septum and point C for the left ventricle." However, in view of the findings of Schmitt and associates[7] and Frank,[8a] this seems unnecessary since human body surface potentials exist as nearly exact mirror patterns which may be canceled against each other, as predicted from a single fixed-location dipole hypothesis.

Two new additional leads were added to a conventional lead selector switch as illustrated by the circuit diagram shown in Fig. 3. The principle of creating a synthetic lead has been described previously.[3,5]

Fig. 4 was derived from the triangle show in Fig. 1, *a* with the addition of three augmented unipolar extremity axes and the two new axes. By using the length of Lead I as a standard of reference, let us set up an octaxial system with a scale which may be used for vector projection methods employing the six extremity leads as now conventionally recorded plus the two new leads described previously. The head-to-foot component of the dipole is really only approximately one-half the magnitude supposed heretofore, that is, the Leads II, III, and aV_F as conventionally recorded are approximately two times as large as they should be from the standpoint of the true manifest vector[4] and require the application of a proportionality factor when using vector methods.[3] The proper

proportionality factor for each lead can be obtained as follows: The length of Lead I divided in turn by the length of each other lead axis gives the proportionality factor to be used in laying out a scale on each lead axis. In other words,

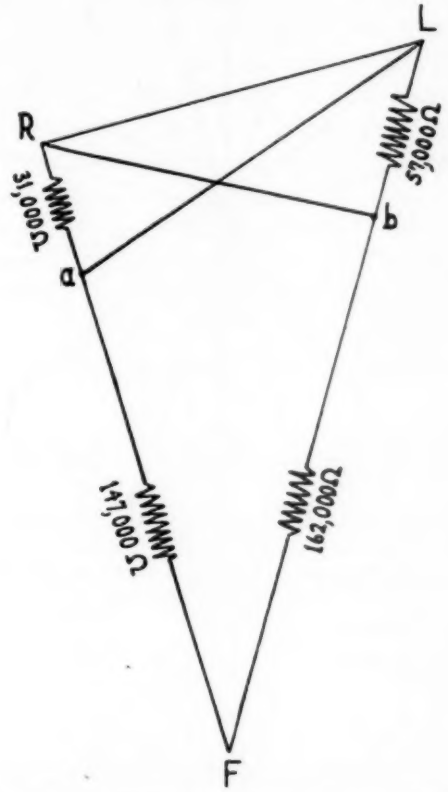

Fig. 3.—A diagram of the method employed to obtain the two synthetic leads. Lead "A" is the potential difference between points *L* and *a*; lead B is the potential difference between points *b* and *R*. All the resistors are large so as not to load the body, but they are small compared to the input resistance of the amplifier. Lower resistances would be less accurate but might have to be considered in laboratories where 60-cycle interference is a problem.

the length of a scale unit on each lead is inversely proportional to the total length of the corresponding lead. The factor for each lead is given in round numbers as follows, reading clockwise from the axes of aV_L: Lead $aV_L = 0.8$, Lead A = 1.0, Lead I = 1.0, Lead B = 1.2, Lead $aV_R = 1.1$, Lead II = 0.6, Lead $aV_F = 0.6$, Lead III = 0.5. It will be seen that Lead III which is twice the length of Lead I in Fig. 1 is assigned a proportionality value of only 0.5. This is so because the vector from which Lead III may be derived by vector projection is by virtue of its position on the image surface twice the length of the vector from which Lead I may be derived, so for purposes of vector projection Lead III requires a correction factor of 0.5 when Lead I has a factor of 1.0. In Fig. 4 the octaxial system is illustrated with units drawn to proper scale for vector projection. The six conventional leads and the two new ones may be projected on Fig. 4 by letting either 1, 2, or 3 mm. in amplitude, respectively, equal one unit of length, or a similarly appropriate choice of area in terms of microvolt seconds may be used.

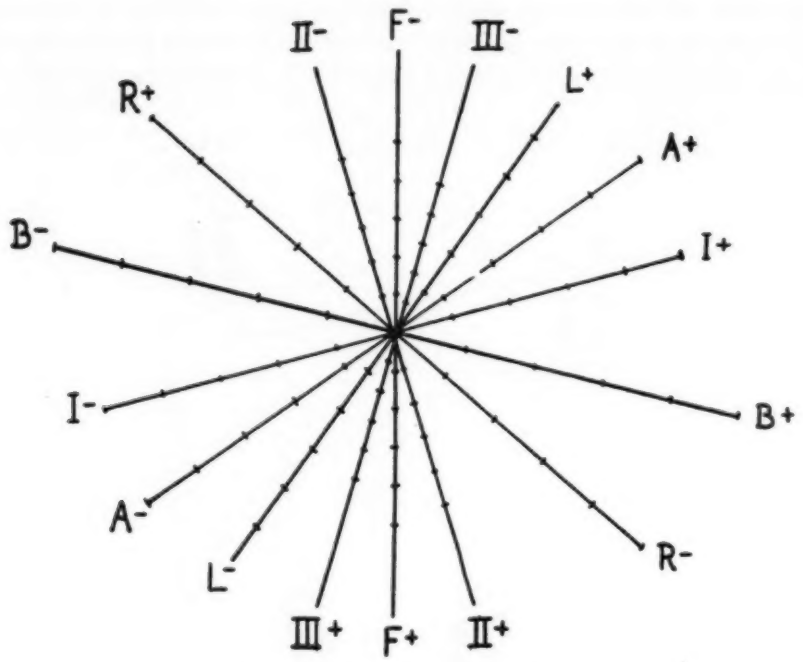

Fig. 4.—The octaxial reference system with the addition of units for vector projection. For explanation see text.

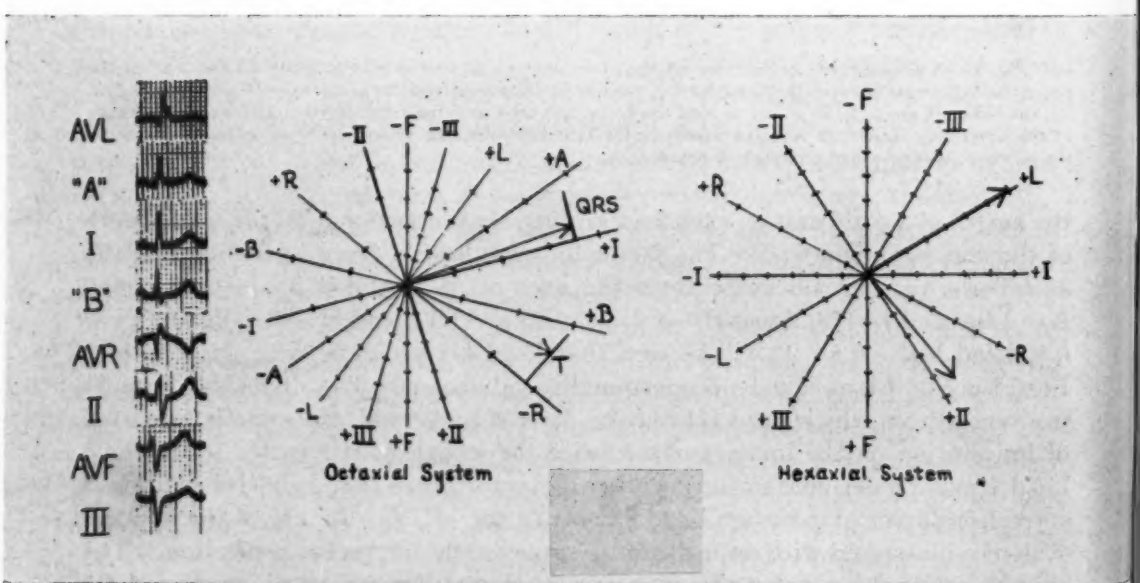

Fig. 5.—Illustrates the application of the octaxial reference system and the comparison of the QRS-T angle obtained by the new octaxial and conventional hexaxial systems. See text.

USE OF THE OCTAXIAL SYSTEM

The direction of the mean QRS and T vectors and the QRS-T angle may be quickly determined by selecting a biphasic or an isoelectric deflection and drawing the vector perpendicular to the axis of this lead just as is done on the conventional hexaxial system.[9,10] However, the octaxial system differs from systems based on the equilateral triangle in that proportionality factors must now be taken into account when dealing with the magnitude of a vector, since a more general and presumably more accurate basis for vector projection is being used. The proportionality scale was described in the last paragraph and is illustrated in Fig. 4. First, let us consider the difference in vector direction and QRS-T angle for various combinations of diphasic deflections in the six conventional limb leads using the new octaxial system as against the old hexaxial system. Table I shows all possible combinations when the mean QRS or T vector direction occurs anywhere from the positive axis of Lead III to the negative axis of aV_F. This range covers most normal and a majority of borderline QRS-T angles.

TABLE I. COMPARISON OF QRS-T ANGLES DETERMINED BY THE EQUILATERAL TRIANGLE SYSTEM AND THE NONEQUILATERAL TRIANGLE SYSTEM

EQUILATERAL TRIANGLE			NONEQUILATERAL TRIANGLE			ANGULAR DIFFERENCE BETWEEN TWO SYSTEMS
DIRECTION OF QRS VECTOR (AXIS)	DIRECTION OF T VECTOR (AXIS)	QRS-T ANGLE (DEGREE)	DIRECTION OF QRS VECTOR (AXIS)	DIRECTION OF T VECTOR (AXIS)	QRS-T ANGLE (DEGREE)	
+III	+F	30	+III	+F	16	−14
+III	+II	60	+III	+II	34	−26
+III	−R	90	+III	−R	66	−24
+III	+I	120	+III	+I	121	+ 1
+III	+L	150	+III	+L	161	+11
+F	+II	30	+F	+II	18	−12
+F	−R	60	+F	−R	50	−10
+F	+I	90	+F	+I	105	+15
+F	+L	120	+F	+L	145	+25
+F	−III	150	+F	−III	164	+14
+II	−R	30	+II	−R	32	+ 2
+II	+I	60	+II	+I	87	+27
+II	+L	90	+II	+L	127	+37
+II	−III	120	+II	−III	146	+26
+II	−F	150	+II	−F	162	+12
−R	+I	30	−R	+I	55	+25
−R	+L	60	−R	+L	95	+35
−R	−III	90	−R	−III	114	+24
−R	−F	120	−R	−F	130	+10
+I	+L	30	+I	+L	40	+10
+I	−III	60	+I	−III	59	− 1
+I	−F	90	+I	−F	75	−15
+L	−III	30	+L	−III	19	−11
+L	−F	60	+L	−F	35	−25
−III	−F	30	−III	−F	16	−14

This table covers the average range for most normal and borderline combinations of mean QRS and T vector directions.

Fig. 5 illustrates the use of the octaxial system to obtain the magnitude and direction of the mean QRS and T vectors in the frontal plane. For the electro-

cardiogram shown in Fig. 5 the QRS-T angle obtained by conventional hexaxial system was 87°, a suspiciously high value which is borderline or slightly abnormal. On the other hand, the QRS-T angle according to the octaxial system appears to be within "normal" limits. The range of normal values using the octaxial system remains to be determined.

THE APPLICABILITY OF THE MEAN QRS-T ANGLE CONCEPT IN VECTORCARDIOGRAPHIC DIAGNOSIS

It is an accepted fact that the amplitude and direction of the T wave as a criterion in diagnosis by pattern electrocardiography bears a relationship to the QRS reflection. For instance, in the presence of right-axis deviation of the QRS, the QRS in aV_L may be inverted and in such a case an inverted T_{aV_L} is normal. However, in case of left-axis deviation of the QRS an inverted T_{aV_L} especially when accompanied by a low, flat, or even inverted T_I is usually abnormal. The use of the QRS-T angle is a compact means of expressing this relationship among the electrocardiographic patterns. The QRS-T angle permits the use of a single number to replace the more complicated and less precise terminology used in describing certain properties of the patterns in the six limb leads.

The fact that the QRS-T angle describes certain QRS-T relationships in the limb leads is invariably true, regardless of the validity of any theorectical hypothesis, provided no error in recording the six extremity leads has been made, since the six leads are a closed system derived from three points that have a fixed and inevitable mathematical interrelation by construction. Because of this relationship among the six extremity leads, data obtained from any two or more of them may be used to define a self-consistent vector in the frontal plane and utilized as such, even if in theory the system has little resemblance to conditions actually existing in the body.[10,11] Therefore, the use of the QRS-T angle should be just as meaningful for certain purposes as interpretation by pattern methods, and it has the advantage of being a shorthand empirical device which simplifies interpretation. However, by the same token its usefulness must be empirically determined.

PURPOSE OF ADDING TWO NEW LEADS IN THE FRONTAL PLANE

One may question the wisdom of increasing rather than decreasing the number of electrocardiographic leads. It is true that for spatial vectorcardiography using the cathode-ray oscillograph only three leads are necessary: horizontal, vertical, and sagittal. However, without the advantage of photographically recorded vector loops, additional leads increase the facility with which the direction of mean vectors for the QRS, T, or any segment of the QRS may be determined from the routine electrocardiogram.

In the frontal plane two leads are sufficient to determine the direction and magnitude of mean vectors. However, to do this accurately the net algebraic areas within the deflection must be carefully determined and vector projection carried out. It must be remembered that the mere use of amplitude of the lead

is a very gross approximation and in some cases may result in serious error since amplitude is not necessarily an accurate measure of area. For many years the three standard limb leads were used for pattern diagnosis and provided a good deal of information. With the advent of the so-called unipolar extremity leads it was possible to construct a hexaxial reference system which made it easier to quantitate the information available in the frontal plane electrocardiogram. However, it should be pointed out that the unipolar extremity leads are of course not truly unipolar but represent a difference in potential between the limbs and the Wilson Central Terminal. Furthermore, they contain no unique information that is not already present in a slightly different form in the three standard leads. However, the estimation of the direction of mean vectors by simple inspection of the leads is much easier when one has six leads than when there are only three.

As we have mentioned previously, the use of a nonequilateral triangle results in a hexaxial reference system in which there are two disproportionately large angles.[3] It seems appropriate to fill in these gaps with additional lead axes. The presence of these two additional leads should further increase the facility with which the mean vectors can be quickly and easily estimated by simple inspection of the leads, just as the hexaxial system was an improvement over the triaxial system for this purpose.

The magnitude of the vector is also more easily obtained by an octaxial system in the following manner. If the direction of the vector is given, one of the two adjacent lead axes being nearly parallel to the mean vector will correspond to the deflection of largest amplitude. It is easier and more accurate to estimate the area of this one large and usually monophasic deflection than of two smaller usually multiphasic ones, as has been done heretofore. The magnitude of this large lead in microvolt seconds is obtained and plotted as a point on this lead axis. The intersection of a line, from this point drawn perpendicular to this lead axis, and the axis of the mean vector gives the magnitude of the mean vector (Fig. 5).

DERIVATION OF THE SPATIAL VECTOR FROM THE IMAGE SURFACE

The direction and magnitude of the mean vector in the transverse plane of the chest leads may be more accurately derived from a reference diagram based upon the image surface of Frank.[4] This will be the subject of a subsequent paper since certain details of dimensions and location of heart dipole remain to be determined in a group of normal individuals. It should then be possible to determine the mean spatial vector more accurately by use of the octaxial system described in this paper for the frontal plane, an image surface diagram for the transverse plane of the chest leads, and a geometric model[12] for the projection of the frontal and transverse plane vectors in space to obtain the resultant mean spatial vector.

SUMMARY AND CONCLUSIONS

1. The use of a nonequilateral triangle for frontal plane vectorcardiography is supported by strong evidence. In this paper we have illustrated the use of this method for the derivation of mean QRS and T vectors. This method may of course be applied to all phases of frontal plane vectorcardiography.

2. The addition of two new axes to the hexaxial system giving an octaxial reference system is recommended. Synthetic leads to accomplish this are described.

3. Since the octaxial system based on the electrical image surface concept involves different angles and proportionality factors than the hexaxial system used heretofore, the range of normal values must be redefined.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

Le uso de un triangulo non-equilatere in vectocardiographia a plano frontal se recommenda per forte argumentos. In le presente articulo nos ha illustrate le uso de iste methodo in le derivation de vectores median QRS e T. Le mesme methodo es naturalmente etiam usabile in omne altere phases del vectocardiographia a plano frontal.

Nos recommenda le addition de duo nove axes al systema hexaxial. Nos describe le derivationes synthetic per que un systema referential a octo axes es obtenibile.

Le systema octaxial es basate super le concepto del superficie del imagine electric. Per consequente illo implica altere angulos e altere factores de proportionalitate que le systema hexaxial previemente usate, e nove definitiones es requirite pro le limites del valores normal.

I wish to acknowledge the invaluable assistance of Ernest Frank, Ph.D., in reviewing the manuscript of this paper and for his help in constructing the octaxial lead selector switch and selecting an appropriate nonequilateral triangle for frontal plane vectorcardiography.

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AN INEXPENSIVE MOBILE VECTORCARDIOGRAPH

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THE present interest in vectorcardiography and the high cost of the equipment have led to the development of a mobile vectorcardiograph which makes use of two standard direct-writing electrocardiographs and a low-priced industrial oscilloscope. The cost, excluding the two electrocardiographs, but including the camera, was about $500.

A block-diagram of the vectorcardiograph is shown in Fig. 1. The electrocardiographs are connected through de-emphasis networks to the input terminals of a pair of external deflection amplifiers. The amplified signals are applied directly to the deflection plates of a cathode-ray tube (CRT). A variable-frequency sawtooth generator acts as a beam interrupter when its output is applied to the control grid of the CRT. Fig. 2 shows the complete vectorcardiograph mounted on a wagon for mobile use, with the amplifiers, beam interrupter, and power supply contained in the cabinet on the lower shelf. A camera is mounted on a hinged support over the oscilloscope screen. The circuit diagram is shown in Fig. 3; it should be noted that a smaller power supply could have been used.

COMPONENTS OF THE VECTORCARDIOGRAPH

The Electrocardiographs.—Because of their availability, the electrocardiographs used were Sanborn Viso-Cardiettes, Model 51. The alterations which were made do not affect their operation for normal use. The first change which was found necessary was the removal of the connection between the right leg lead and the lowest wiper of the lead-selector switch. Without this alteration, there would be interaction between the two electrocardiographs unless the lead selector switches were at the same settings, so that recordings for different planes could only be made by changing the leads at the patient. The modification permitted any combination of lead selections to be made, and the circuit then corresponded to that found in multi-channel recorders such as the Sanborn Twin-Beam Cardiette, Model 62.

The second alteration was to short out the ½-megohm resistor in series with the slider of the sensitivity-control potentiometer in each electrocardiograph to allow the sensitivity to be reduced to zero. It was found to be simpler to control the amplification at this point than in the deflection amplifier.

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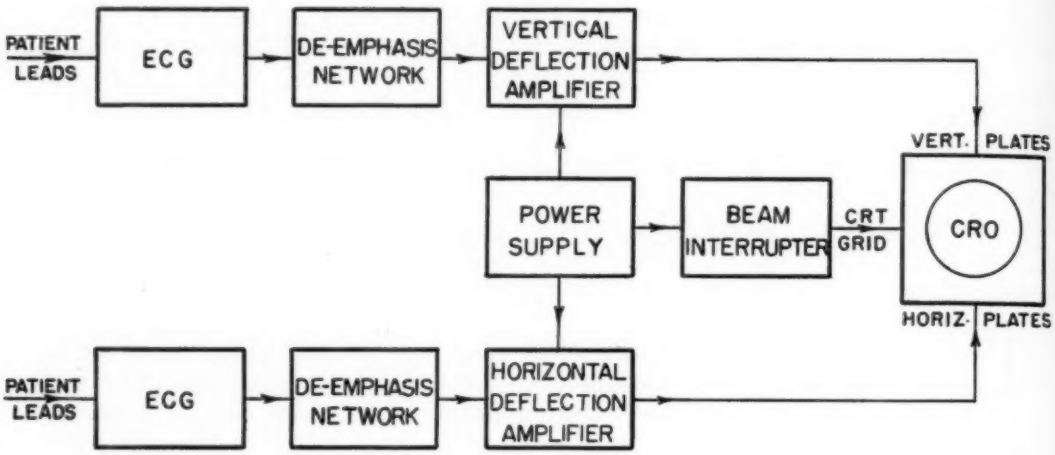


Fig. 1.—The block-diagram of the vectorcardiograph.

Fig. 2.—The mobile vectorcardiograph. The output from the two electrocardiographs passes to the deflection amplifier on the lower shelf, and thence to the deflection plates of the oscilloscope. The controls at the left are for the beam interrupter. The camera can be seen in the box above the oscilloscope.

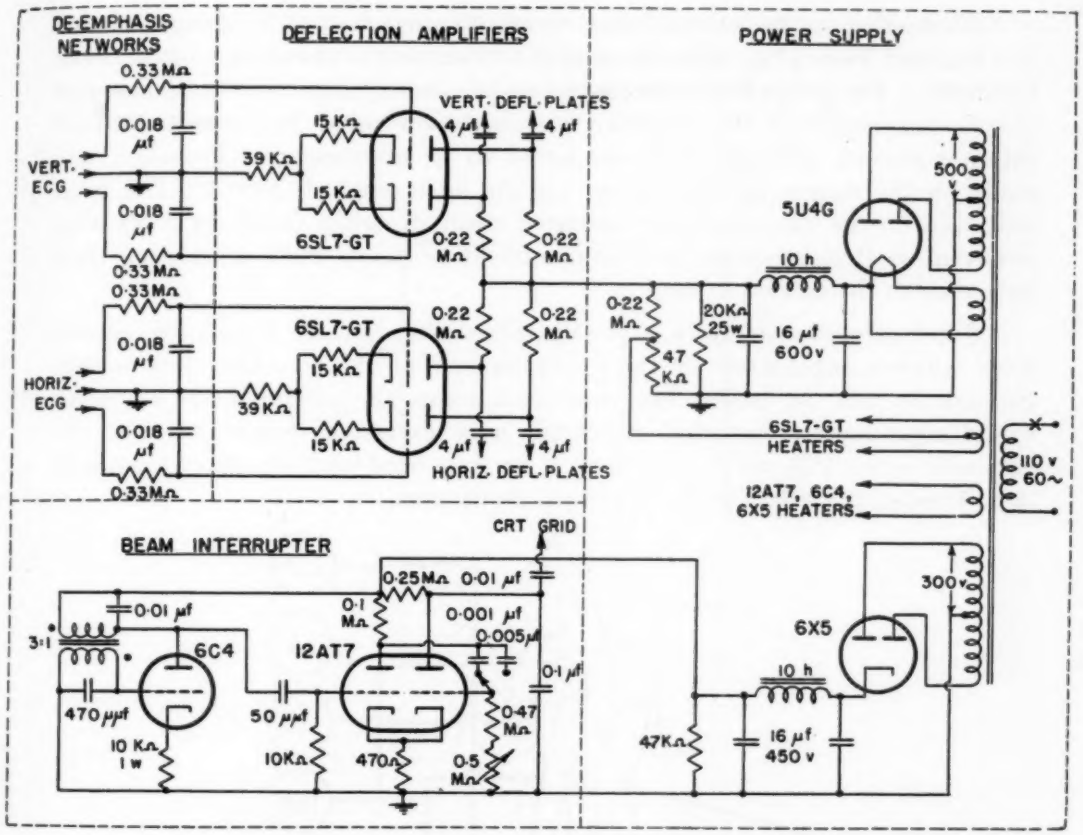


Fig. 3.—The circuit diagram.

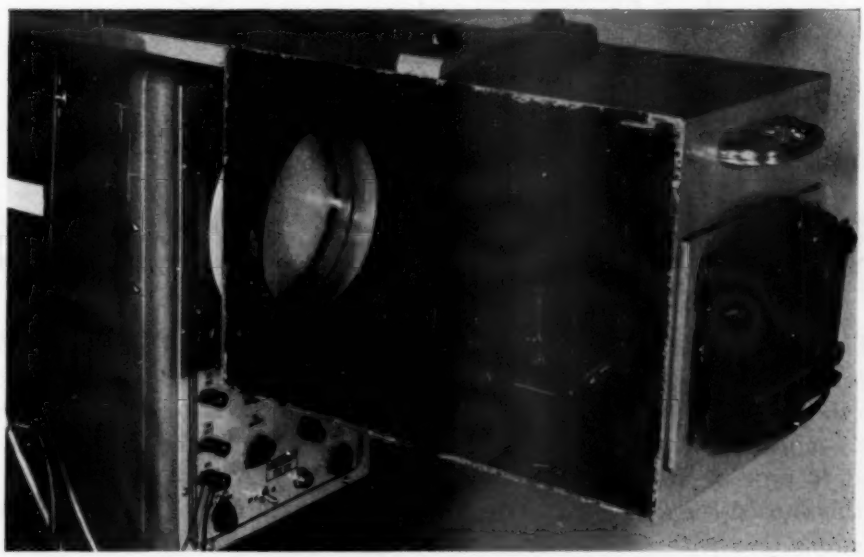
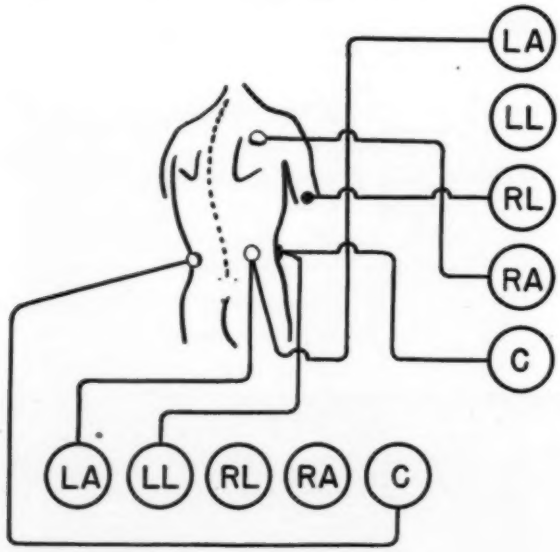


Fig. 4.—The camera in its mounting. The side of the camera box has been removed. Once set the focus of the camera never needs to be altered and the only control is a cable release, not shown.

Connection to the galvanometer terminals was effected by using two pins of a four-pin Jones plug, with the third pin connected to the chassis of the Viso-Cardiette. The grounding leads for the electrocardiographs and the oscilloscope chassis terminated at the amplifier chassis, which could be connected to an external ground, although this was found to be unnecessary. Provision was made on the wagon for four power outlets on a single line-cord. The neon indicators on the Viso-Cardiettes operated normally, when the Jones plugs were removed, so that the usual precautions could be taken when connecting their line-cords to the power outlets.

The De-emphasis Network.—The Viso-Cardiettes contain a pre-emphasis network which compensates for the characteristics of the recording mechanism. Because of this, an oscilloscope connected across the galvanometer terminals would reproduce a distorted waveform with excessive overshoot. The de-emphasis network shown in Fig. 3 is that recommended by the Sanborn Company to counteract the effects of the pre-emphasis network.



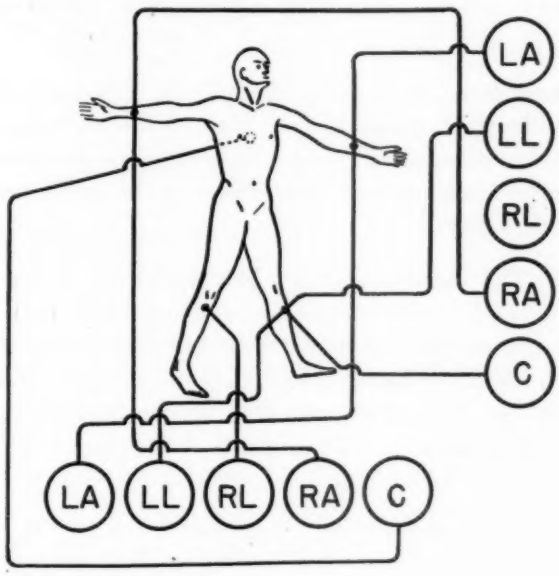
A.

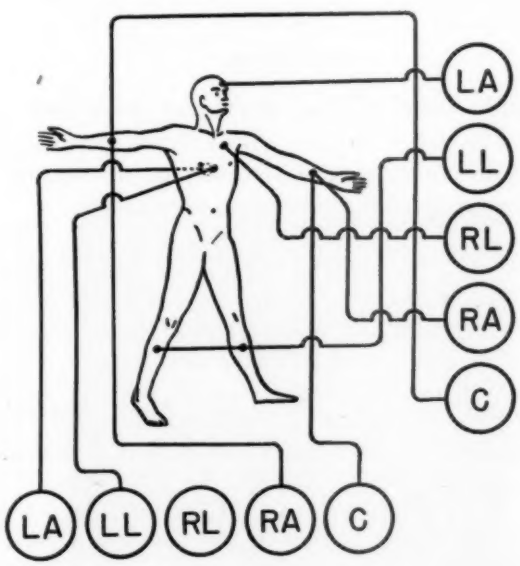
Fig. 5.—The methods of connecting the patient to the electrocardiographs, in Grishman's system (*A*), Wilson's system (*B*), and a system used by one of the writers (*C*). The circles in horizontal rows correspond to the patient-cable connectors of the electrocardiograph acting as the horizontal amplifier, while those in vertical rows correspond in a similar way to the other electrocardiograph.

The Deflection Amplifiers.—The amplifiers were designed to permit direct connection through the de-emphasis networks to the galvanometer terminals, at which there is a static potential of 70 volts with respect to the chassis. However, direct connection of the deflection plates of the CRT to the amplifier anodes tended to produce marked defocussing. The blocking capacitors used to prevent this caused the anode circuits to have time constants of at least 16 seconds. In combination with the 2-second time constants of the Viso-Cardiettes, the over-all time constants became roughly 1.7 seconds, which does not produce significant alteration of the decay curve.

Each amplifier was designed to produce a deflection of approximately four inches of the electron beam for a stylus movement of 0.5 cm. on the direct writer; however, this could be increased threefold, or more if necessary, by a change of resistor values in the cathode circuit.

B.





C.

Fig. 5, *B* and *C*. *(For legend see opposite page.)*

The Oscilloscope.—A Sylvania Type 1322 oscilloscope was chosen because it was relatively inexpensive, it had a 7″-diameter tube (7JP1), and terminals were available at the rear for direct connection to the deflection plates and to the control grid.

The only modification of the oscilloscope was the removal of the plastic grid mounted behind the protective glass window. This grid was cut as shown in Fig. 2 and placed in front of the window when adjusting the sensitivity controls for equal gain.

The Beam-Interrupter Circuit.—The beam-interrupter circuit shown in Fig. 3 was used to provide time markings on the vectorcardiograph loop. It was chosen in preference to other similar circuits[1] because of its stability of calibration and ease of control. There was no interaction of the oscilloscope controls upon the frequency of oscillation.

The Camera.—The camera was an old Voigtlander, fitted with a Wollensak 101 mm. f4·5 lens, and modified to take 3¼″ × 4¼″ sheet film. An expensive camera is not needed, the only requirements being that it should be able to focus up to about 17 inches, that it should have a cable release, ground-glass focusing, and an f4·5 lens, and that it should take sheet film holders, 3¼″ × 4¼″ being large enough. The details of the camera mounting are shown in Fig. 4.

It was found that good photographs of the trace on the P1 screen could be obtained with Kodak Royal film; Kodak Super XX gave fairly good results. The developer used was Kodak DK50.

OPERATION

Patient Connections.—Standard limb electrodes were used although a second binding post was added to two of them. Fig. 5 shows the connections for Grishman's system[2] (*A*), Wilson's system[3] (*B*), and for a system which one of the writers (GED) has been using with satisfactory results (*C*).

Amplifier Connections.—The output terminals from the amplifiers were connected to the oscilloscope deflection plates so that pressing the 1 mv. standardization button on one Viso-Cardiette moved the electron beam to the right and pressing the button on the other moved it downward.

Use of Lead Selector Switches.—The lead selector switches can be used to change from one plane to another; the appropriate lead selections are indicated in Table I.

Standardization.—The amplification required is such that a satisfactory loop is obtained; this can be achieved by adjustment of the sensitivity controls on the Viso-Cardiettes. After having obtained the desired approximate size of loop, it is important to ensure that distortion is not being produced by unequal amplification on the two axes. This may be done by setting the lead-selector switches

TABLE I. LEAD SELECTIONS ON ELECTROCARDIOGRAPHS TO OBTAIN DIFFERENT PLANES

SYSTEM	PLANE	SETTINGS OF LEAD SELECTOR SWITCHES	
		HORIZONTAL AMPLIFIER	VERTICAL AMPLIFIER
Grishman (Fig. 5A)	Frontal	CL	1
	Horizontal	CL	CL
	Sagittal	3	1
	Standardization	3	CL
Wilson (Fig. 5B)	Frontal	1	V
	Sagittal	V	V
	Standardization	1	1
G. E. D. (Fig. 5C)	Frontal	CR	3
	Horizontal*	3	CR
	Sagittal	3	3
	Standardization	CR	CR

*For this horizontal plane to correspond with the orientation of Grishman's horizontal plane the finished photograph should be turned clockwise through 90° before inspection.

to the standardization settings indicated in Table I, so that equal patient voltages are supplied to the two electrocardiographs and a linear trace appears on the screen of the cathode-ray tube. The sensitivity controls on the Viso-Cardiettes are adjusted until the trace is inclined at an angle of 45° with the horizontal axis. The easiest way to measure this angle is to use the plastic grid which was removed from the oscilloscope.

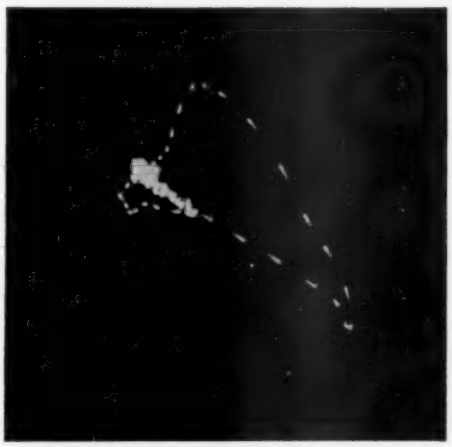


Fig. 6.—Shows a specimen tracing: a frontal plane vectorcardiogram, using Grishman's system.

Any desired relative gain can be obtained by using the appropriate angle given by

$$\tan \theta = y/x$$

where θ is the angle which the trace makes with the horizontal, and y/x is the relative gain (vertical/horizontal).

Centering Controls.—The centering controls on the Viso-Cardiettes should be adjusted to center their styluses, and the oscilloscope controls should be used for positioning the loop. A slight inconvenience is encountered as a result of the long time-constant of the deflection amplifiers.

Setting the Beam Interrupter.—With the interrupter used, the trace is inscribed in the direction of the blunt end of the spot. The interruption frequency should be adjusted to give satisfactory detail for the portion of the tracing being examined. An interruption frequency of about 800 or 1000 c.p.s. is usually suitable for timing the QRS sÊ loop whereas interruptions of approximately 80 c.p.s. are better for the study of the T sÊ loop.

Taking the Picture.—When a satisfactory trace has been obtained, the camera shutter is set to "bulb", the camera is swung down opposite the face of the tube, and a film is inserted. The paper drive on one Viso-Cardiette is then started. When to open and close the shutter is then determined by watching the electrocardiographic tracing. With a little practice this becomes quite easy, even with patients who have atrial fibrillation. Fig. 6 shows a specimen tracing.

SUMMARIO IN INTERLINGUA

Esseva construite un mobile vectocardiographo per medio de un oscilloscopio industrial con un tubo de 7 pollices de diametro. Isto esseva activate via un par de amplificatores de deflexion per duo electrocardiographos a registration directe. Le costo—ultra le electrocardiographos sed includente le camera—esseva circa 500 dollars. Le amplificatores esseva specialmente construite pro assecurar un minimo de distortion general. Lor capacitate amplificatori excedeva per multo le grado necessari pro le complete deflexion del fasce electronic. Leve modifications del electrocardiographos esseva requirite, sed istos non afficeva lor efficacia normal in ulle maniera.

Es describite un methodo pro obtener varie planos vectocardiographic per medio del selectores de derivation in le electrocardiographos.

Le construction e activation del apparatura es describite in complete detalios.

We wish to thank Dr. M. B. Walters for his support and advice, and Mr. F. McGillivary for his technical assistance.

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MUSCULOSKELETAL CHEST PAIN FOLLOWING MYOCARDIAL INFARCTION

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THE index of suspicion of myocardial infarction has risen abruptly during the past few decades. Accompanying this increased awareness have been the knowledge that an individual with arteriosclerotic heart disease is likely to have several episodes of myocardial infarction during his lifetime and the tendency of the physician to stress the importance of the symptom of chest pain to the patient. Therefore, any chest pain occurring after the pain of myocardial infarction, and even remotely similar to it, is frequently interpreted by the patient as a symptom of serious heart disease.

Persistent pain in the shoulder following myocardial infarction was first discussed at length by Edeiken and Wolferth in 1936.[1] The hand component of the disorder, now commonly recognized as the shoulder-hand syndrome, was described in 1940 by Ernstene and Kinell,[2] and by Askey in 1941.[3] Since it is estimated that 12 to 21 per cent[1,2,4] of patients following myocardial infarction develop some degree of disability of the shoulder or hand, the disorder is of considerable importance.

Less attention has been paid to pain in the chest persisting after myocardial infarction, and behaving somewhat like angina pectoris, coronary insufficiency, or repeated attacks of infarction. Although similar pains have been mentioned in isolated cases,[5-7] no comprehensive discussion of the characteristics of the pain could be found. In 1928, Eckerson and associates[8] reported four patients who, after myocardial infarction, continued to have a persistent sense of pressure or actual pain in the anterior chest. This pain was delayed in onset following exercise or emotional stress as compared to anginal pain, and was attributed to the presence of the myocardial scar. Similar chest pain has been encountered here in eight of sixty referred patients with myocardial infarction—an incidence of 13 per cent. It is the purpose of this communication to describe this variety of chest pain, the mechanism of which is unknown.

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CLINICAL FEATURES

Of sixty referred patients with myocardial infarction, either acute or old, eight had persistent chest pain. One patient with chest pain had pain in the shoulder and hand in addition; two other patients in this series had developed the shoulder-hand syndrome without chest pain.

The onset of the chest pain occurred within the first two weeks following myocardial infarction in six of the eight patients, three months later in one, and six months later in the other. The pain was located in the left precordium in six patients, and spread to the entire anterior chest wall in two patients. The postinfarction pain was located in the same area as the pain of the acute infarction in one-half of the patients. The onset of the pain was gradual, and its duration varied from 30 minutes to several days, usually about 1 to 2 hours. It was most often described by the patient as a steady, dull, aching, or pressing pain. The intensity of the pain was usually mild to moderate. However, in two patients in whom the pain came on within the first week after infarction, it was so severe that opiates were required for relief. The episodes of pain recurred intermittently duing a period of time varying from one month to three years.

There was no specific relationship to generalized physical exertion except that the pain was likely to occur toward the end of the day when the patient felt fatigued. In five of the eight patients the pain was worse lying down, especially if lying on the left shoulder. Seven of the patients could relate either the onset or the aggravation of the pain to a specific movement of the body or arm: four to raising the arms above the head, and three to a turning or twisting motion of the body. Although none described a pleuritic pain, in three patients the pain was made slightly worse by taking a deep breath. Nitroglycerin had no effect on the pain in any of the patients, and in none of them did physical exertion reproduce the pain.

Six of the eight patients were found to have localized areas of muscle tenderness within the area of the pains. However, the exact spontaneous pain was not reproduced by pressure. Reproduction of the spontaneous pain was accomplished in all but one patient, either by raising the arms high over the head or by twisting the body.

Other sources of skeletal pain were sought in all of these patients. In one there was definite rheumatoid arthritis of the hands and spine with superimposed osteoarthritis in the cervical spine, leading to intermittent pain in the back of the neck. This patient was the only one of the group with pain located in an area other than in the anterior chest, having both anterior chest and posterior neck pain simultaneously.

Three of the eight patients had angina pectoris occurring after myocardial infarction. Two of them were unable to differentiate the attacks of angina from the skeletal chest pain until after the exercise test separated the short-lived anginal pain from the prolonged skeletal pain. Another noted that his skeletal pain became much more severe during periods of increasingly frequent attacks of nocturnal angina.

Rinzler and Travell[9] have shown in four patients that local procaine infiltration or topical ethyl chloride spray may dramatically benefit this type of local pain; these measures were not deemed necessary in the patients in this series. Reassurance that the pain was not serious, local heat, and analgesics have allayed the anxiety concerning the pain and reduced its intensity, although most of the patients have continued to have milder discomfort at less frequent intervals.

REPORT OF CASES

A 54-year-old barber had been previously in fair health until three weeks prior to being seen here, when he had suddenly developed an excruciatingly severe squeezing pain located deep to the entire anterior chest and radiating to the back of the neck, the left shoulder, and the left arm. The initial electrocardiogram revealed a large acute anterior myocardial infarction. For the next two weeks, while in another hospital, he continued to have the same pain in variable degrees of severity, being free of pain only for short periods after narcotic injections. On the day of admission here, the pain had again become excruciating and had not been entirely relieved by morphine.

For the past three years the patient had noted intermittent swelling in the fingers, wrists, elbows and shoulders, with persistent rheumatoid deformities of the fingers. Both cortisone and Butazolidin had given relief during the more acute attacks. On several occasions he had also developed severe pain in the neck, with a lancinating pain radiating down the left arm on motion of the neck. X-ray films of the cervical spine had revealed minimal rheumatoid changes, with marked osteoarthritis superimposed. The neck and arm pain had responded to cervical traction. Because of these previous difficulties, both cortisone and neck traction had been tried during the past two-week period without benefit.

On admission the patient was confused, hyper-reactive and screaming with pain. The blood pressure was 120/80 mm. Hg and the pulse 100 per minute. Pressure over the spinous process of the fourth and fifth cervical vertebrae, as well as pressure over the fifth rib 5 cm. to the left of the sternal border, made his pain worse. The heart sounds were quite faint; there was no cardiac enlargement or friction rub. No signs of congestive failure were present. A moderate rheumatoid deformity of the fingers was noted; the hands were cool and moist.

The electrocardiogram again revealed an acute massive anterior myocardial infarction. The fedimentation rate was 37 mm./hour; the white blood cell count 7,350, with 70 per cent segmented forms. Morphine, ¼ grain, relieved his pain initially, and the patient was begun on Dicumarol and a low-salt diet. After the initial morphine the blood pressure gradually fell over a two-hour period to 94/70 mm. Hg. At this time a sublingual tablet of glyceryl trinitrate, 1/200 grain, caused a further decline in blood pressure to 74/64 mm. Hg, and marked coldness and clamminess of the patient's skin. A continuous intravenous infusion was then instituted, delivering glyceryl trinitrate at the rate of 1/200 grain per hour, and norepinephrine at a rate sufficient to maintain the blood pressure at 120/80 mm. Hg. On the third hospital day digitalization was begun because of an inconstant protodiastolic gallop and basilar pulmonary râles which disappeared 24 hours later. By the fifth day, the patient was able to maintain a blood pressure of 120/80 mm. Hg without norepinephrine while receiving nitroglycerin, 1/200 grain, sublingually every two hours during the day, and Nitrol ointment, 2 inches, rubbed into the skin at bedtime. Also, on the third day, it was noted that the apical pulsation had gradually become quite diffuse and forceful, whereas it had been almost imperceptible on admission. A transient ventricular aneurysm was postulated, and was probably confirmed by the fact that the abnormally forceful and diffuse pulsation gradually disappeared by the twelfth hospital day.

The patient had continued to have two to three attacks daily of severe left chest-wall pain, radiating to the left shoulder and back of the neck. The pain lasted one to three hours, usually occurred just before breakfast and at about 8:00 P.M. in the evening, was not related to the time of nitroglycerin administration, and required meperidine or morphine for relief. At about the end of the first week in the hospital an area of tenderness over the fourth rib 4 cm. to the left of

the sternum was noted. As the pain continued, its location became limited to a much smaller area of the precordium just inferior to the left nipple, and its severity gradually diminished.

On the tenth hospital day the patient had a recurrence of his previous lancinating pain down the left arm associated with a marked increase of pain in the back of the neck. On the fifteenth day he had a reactivation of his rheumatoid arthritis, with swelling and pain in the fingers, and pain in the wrists and elbows. ACTH gave him relief from these pains within another week.

By the twenty-second day the patient was having pain only in the left precordium, usually occurring after he became tired toward the end of the day, and lasting one to two hours. Nitroglycerin had no effect on the pain; opiates were no longer required. Pressure on the left fourth rib reproduced the pain, and during the pain twisting and turning motions of his body made the pain worse. Local heat and massage over the left precordium were quite effective in giving relief. The patient was discharged and has done well for the past six months, having returned to work. He continues to have mild episodes of anterior chest-wall pain precipitated by slight fatigue, and relieved by heat and massage.

Comment.—This patient illustrates the gradual transition from cardiac to skeletal pain following myocardial infarction. His pain is an example of a skeletal pain which was not only the source of anxiety regarding serious heart disease but was also an extremely painful disorder in itself.

A 39-year-old gasoline station owner had been in good health until four months prior to his first visit, when he had had a typical myocardial infarction. This episode was characterized by the sudden onset of a steady, pressing, deep pain beneath an area 10 cm. in diameter, located inferior to the left breast, which radiated to the teeth and throat, and persisted 24 hours. The electrocardiogram showed the classic changes of a posterior myocardial infarction, and the laboratory data confirmed the presence of tissue destruction. An uneventful recovery was made, and the patient was discharged from the hospital after three weeks.

Two months after the infarction, when he had resumed partial business activity, he noted the onset of a second chest pain. It began in the early evening after an emotionally upsetting day and built up in intensity slowly over a two-hour period. The location of the pain was in the same area as that of his previous infarction, and it felt deep, steady, and pressing, eventually becoming quite severe. Nitroglycerin gave no relief; opiates were followed by disappearance of the pain in 30 minutes, although they were administered more for the relief of anxiety concering the pain than for its actual discomfort. He was re-admitted to the hospital, but no evidence of myocardial infarction was found. Subsequently, he had five similar pains within the next two months, each beginning in the evening while he was propped up to read in bed. He had noted during this time that raising his arms above his head produced a qualitatively similar discomfort not nearly so severe. These recurrent pains led to great anxiety on his part, since they felt like the pain of his previous infarction, yet his physician could find no evidence of recurrent infarction.

Physical examination revealed tenderness along the fourth rib, 4 cm. to the left of the sternal border. Pressure there was uncomfortable but did not reproduce the exact character of his spontaneous pain as did raising the left arm over his head. The remainder of the examination revealed no further abnormalities.

The electrocardiogram revealed evidence of an old posterior myocardial infarction. Vigorous exercise did not change the electrocardiogram and did not produce pain in the chest.

The patient was reassured that his recurrent attacks of pain were skeletal in origin and did not represent cardiac pain. He was advised not to prop himself in bed to read, and to use local heat and massage for future attacks.

Comment.—This patient illustrates the anxiety caused by skeletal pain when it simulates in some respects the pain of myocardial infarction. Although the patient was told after each recurrence of pain that he probably had not had another myocardial infarction, his fears had not been allayed by an explanation of the source of a pain which he considered too similar to that of his initial attack of infarction to be innocuous.

DISCUSSION

The persistence of chest pain for months after the disappearance of evidence of tissue destruction following myocardial infarction distinguishes this pain from that of acute infarction. However, when the pain comes on within the first week after an infarction, the differential diagnosis between skeletal pain and a second infarction or coronary insufficiency is difficult. The lack of specific relationship of the pain to exertion, the absence of electrocardiographic changes during the pain, the absence of response to nitroglycerin, and its reproduction by arm or body motion, clearly differentiate it from angina pectoris.

Eckerson and associates[8] suggested that the persistent chest pain in his patients was due to the presence of a myocardial scar. It is conceivable that the pain of myocardial infarction or its scar initiates a form of reflex sympathetic dystrophy (causalgia), involving continued nerve discharge, both afferent and efferent, between the heart, central nervous system, and thoracic wall structures, representing a mechanism similar to that postulated for the shoulder-hand syndrome.[9-11] The earlier concept of splinting of muscles in disuse, first postulated by Howard[12] for the painful shoulder after myocardial infarction and later by Ernstene and Kinell,[2] could also be applied to the chest-wall muscles. Although both disuse and reflex dystrophy may be active etiologically, there is no experimental method to prove their respective roles. The fact that twisting motions of the body often reproduce this pain suggests a third possibility, i.e., sensitization, by afferent impulses from the heart, of a pre-existing localized musculoskeletal disorder, so that symptoms from the localized disorder occur only after myocardial infarction.

Skeletal chest pain following myocardial infarction is almost uniformly interpreted by patients as serious cardiac pain, and because of the difficulties of differential diagnosis, physicians are apt to be misled in like fashion. Therefore, the importance of this pain is its differentiation from myocardial infarction and angina pectoris. This can be accomplished by applying those measures in history taking and observation which elucidate skeletal pain.

SUMMARY

1. Musculoskeletal chest pain was encountered in eight of sixty patients following myocardial infarction.

2. The characteristics of the pain are described, and its differentiation from cardiac pain is discussed.

3. The skeletal chest pain usually presents to the patient the problem either of anxiety concerning serious heart disease or, in fewer instances, of an extremely painful disorder.

4. Although the mechanism of the pain is unknown, it seems likely that afferent impulses from the heart following myocardial infarction "sensitize" a localized musculoskeletal disorder in the somatic reference area of cardiac pain.

SUMMARIO IN INTERLINGUA

1. Pena musculoskeletic del thorace post infarcto myocardiac esseva observate in 8 inter 60 patientes.

2. Es describite le characteristicas del pena. Su differentiation ab pena cardiac es discutite.

3. Generalmente iste genere de pena skeletic del thorace representa pro le patiente un causa de anxietate in tanto que ille lo interpreta como signo de un seriissime morbo cardiac. In minus numerose casos le pena mesme es severissime.

4. Le mechanismo del pena non es cognoscite, sed il pare probabile que impulsos afferente, que emana ab le corde post infarcto myocardiac, resulta in le "sensibilisation" de un disordine musculoskeletic in alicun loco restringite intra le area de referentia somatic de penas cardiac.

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THE DIAGNOSIS OF MITRAL INSUFFICIENCY

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THE diagnosis of mitral insufficiency remains a difficult clinical problem in many patients. As surgery so far has very little to offer these cases, every effort should be made to achieve a correct preoperative diagnosis.

The left-heart catheterization with pressure measurement in the left atrium and the left ventricule has opened new diagnostic possibilities. When the pressure curve from the left atrium suggests a significant regurgitation, we can perform a selective angiocardiography through the needle in the left atrium in order to visualize the mitral valves.

METHOD

The technique has been described earlier[1,2] for the introduction of a needle of 1.0 mm. inner diameter (Stille, Stockholm) paravertebrally above the posterior end of the right ninth rib and then into the left atrium. A fine plastic catheter of 0.5 mm. inner diameter is then introduced through the needle into the ventricle and out into the aorta. Pressure measurements are then made, while the catheter is slowly withdrawn from the aorta via the left ventricle to the left atrium. A Warburg-Hansen capacitance manometer is used.

Then the contrast medium is injected through the needle into the left atrium. The injection of 50 to 70 ml. contrast medium has in all cases been performed with an automatic pressure syringe (Gidlund) in 1 to 2 seconds. Due to the oblique position of the atrioventricular plane the patient is investigated in the right oblique position with the central beam directed 20 degrees toward the head of the patient.

RESULTS

The results obtained will be illustrated by the following case. A 25-year-old woman had acute rheumatic fever in 1948. In 1953, she began to complain about precordial pain. There was a harsh systolic murmur audible over the whole heart. A short diastolic murmur was heard over the apex. X-ray investigation showed an enlarged left atrium. The heart was slightly enlarged,

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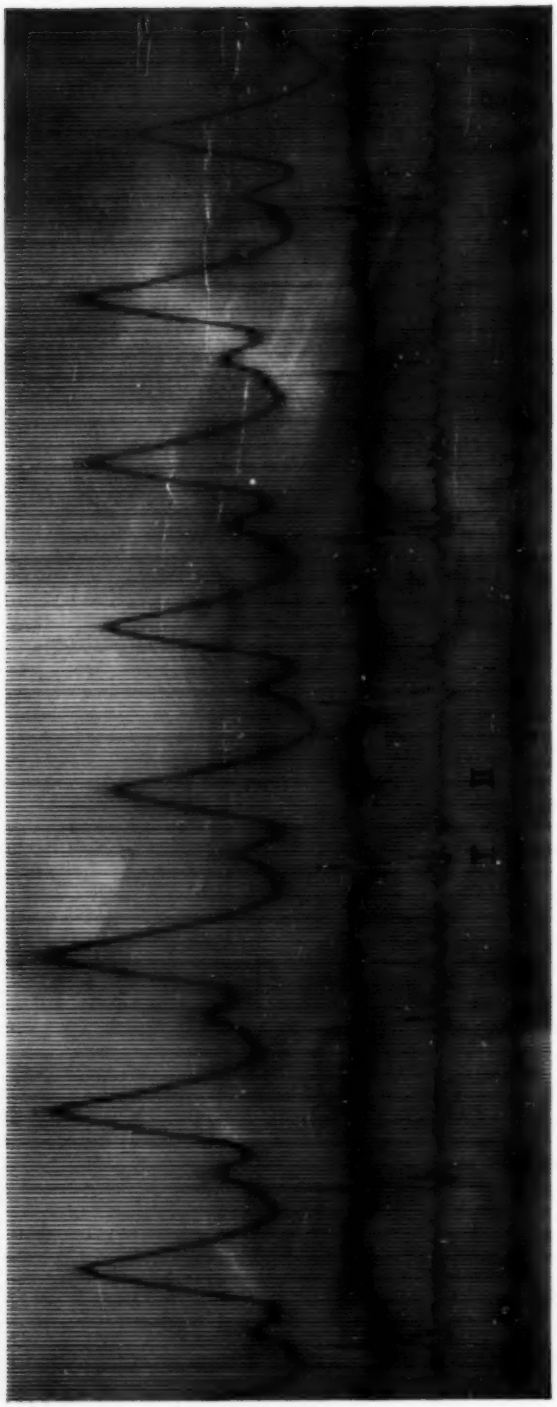
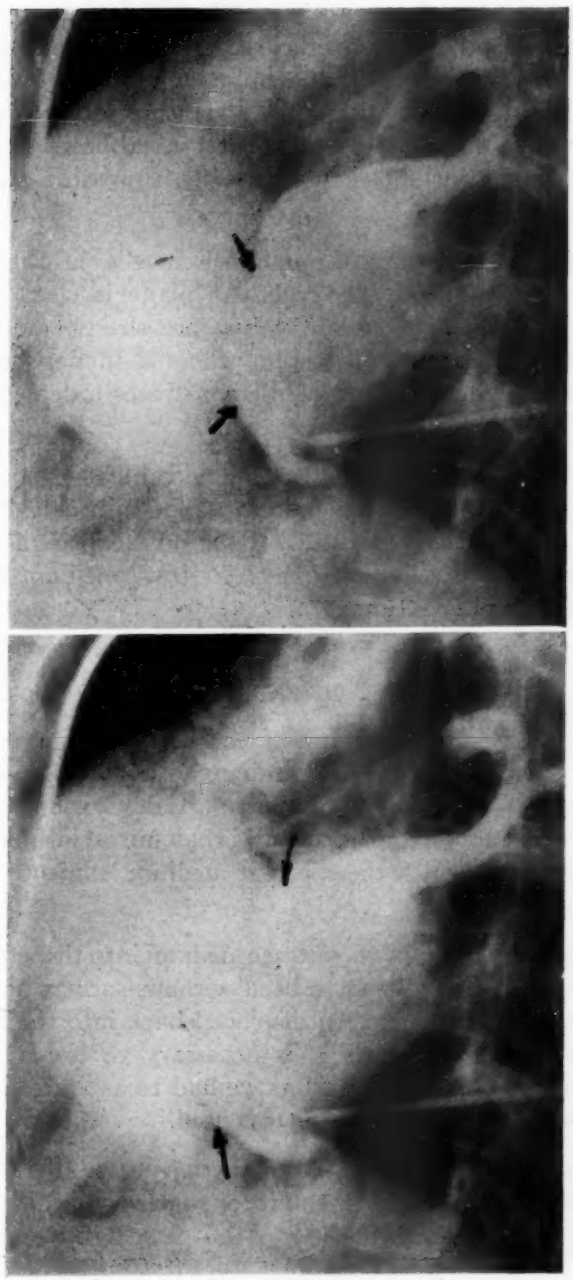


Fig. 1.—Left atrial pressure curve obtained directly through a needle. Mean pressure 11 mm. Hg. *A*, Electrocardiogram. *B*, Phonocardiogram. I = The first heart sound. II = The second heart sound. The pressure peak at the second heart sound is typical for mitral insufficiency.

A.



B.

Fig. 2.—*A*, Angiocardiogram during ventricular systole with contrast injection in the left atrium. An incomplete closure of the mitral leaflets is observed. *B*, Angiocardiogram during diastole with contrast injection in the left atrium. The posterior leaflet (lower arrow) is now visible close to the ventricular wall. The anterior mitral leaflet (upper arrow) has only slightly changed its position. No stenosis of the mitral orifice was thus found.

820 ml. corresponding to 520 ml. per square meter body surface. Electrocardiography was normal with sinus rhythm. Electrokymography suggested mitral stenosis without signs of mitral insufficiency. Her working capacity was 500 kgm./min. The mean pressure in the pulmonary artery was 19 mm. Hg at rest and 25 mm. Hg during exercise. The mean pressure in the left atrium was increased, 11 mm. Hg. The contour of the left atrial pressure curve was typical for a dominating mitral insufficiency with a high pressure peak at the second heart sound, Fig. 1.

Selective angiocardiography through the needle in the left atrium was performed, Fig. 2, *A* and *B*. The valvular plane is clearly outlined during ventricular systole (Fig. 2, *A*). The valves are sharply outlined against the left atrium except in the central portion where a funnel-shaped extension of contrast medium into the left ventricle demonstrates a defective closure of the valves.

During diastole, Fig. 2, *B*, the posterior mitral leaflet is visible close to the ventricular wall (lower arrow) while the anterior mitral leaflet (upper arrow) has changed its position only slightly. Thus no stenosis of the mitral orifice was found. There was a regurgitation of contrast medium to the pulmonary veins from the enlarged left atrium.

DISCUSSION

Angiocardiography with injection of contrast medium through a catheter in the pulmonary artery will clearly outline the left atrial wall permitting the diagnosis of a mural thrombus or an intra-atrial myxoma. To visualize the mitral leaflets clearly enough for the diagnosis of a mitral insufficiency a technique has been worked out by which the contrast medium is injected directly into the left atrium through a needle.

We have tried the injection of contrast medium into the left ventricle through the plastic catheter. So far we have been without success as in every instance the catheter due to a recoil has been displaced back into the left atrium or into a pulmonary vein. Furthermore, it is necessary to use a larger needle and catheter which we do not recommend as we had to aspirate the pericardium for blood in two cases where this technique was used.

So far the patients have had severe reactions after this x-ray investigation, and therefore we do not yet recommend it for routine clinical use.

SUMMARY

When the clinical findings and the left-heart catheterization suggest a dominating mitral insufficiency we can perform an angiocardiography by injection of contrast medium through the needle into the left atrium in order to visualize the mitral valves. By this method it is possible to prove the diagnosis of a mitral insufficiency and avoid an exploratory cardiotomy.

SUMMARIO IN INTERLINGUA

Quando le constatationes clinic e le catheterisation sinistrocardiac suggere un dominante insufficientia mitral, il es possibile render le valvulas mitral angiocardiographicamente visibile per injicer un substantia de contrasto via le agulia a in le atrio sinistre. Iste methodo permitte le verification del diagnose de insufficientia mitral sin cardiotomia exploratori.

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EBSTEIN'S DISEASE WITH WOLFF-PARKINSON-WHITE SYNDROME

Report of a Case With a Histopathologic Study of Possible Conduction Pathways

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WE HAVE encountered a case of congenital heart disease which presented clinically a Wolff-Parkinson-White syndrome and which pathologically proved to be a case of Ebstein's disease. This afforded an opportunity to study histopathologically the various possible conduction pathways, and thus shed light on the anatomic base of the Wolff-Parkinson-White syndrome.

CASE REPORT

C. H., a white boy, was admitted to Children's Memorial Hospital on June 1, 1949, at the age of 9 days. He had been born at full term with a weight of 7 pounds, 9 ounces (3,430 grams). Cyanosis was observed 12 hours after birth and persisted until his admission, even though he had received oxygen continuously.

Physical examination on admission revealed slight cyanosis. The cardiac apex was in the fourth left intercostal space at the nipple line. No murmur was heard. The second pulmonic sound was of normal intensity. Anteroposterior and oblique films of the chest showed the heart to be boot-shaped, with a clear pulmonary window and diminished vascularity of the lung fields. The red cell count was 4.72 million, the hemoglobin 17 grams. The electrocardiogram revealed the presence of the Wolff-Parkinson-White syndrome (Fig. 1). The patient gradually improved to the point where oxygen was no longer necessary, and he was discharged home on August 3, 1949.

Three weeks later, he was brought to the Outpatient Clinic for a routine checkup. The mother stated that he had been doing fairly well, though he was still blue, and became tired before finishing his bottle. Examination at this time revealed a heart rate of approximately 240 per minute. He was readmitted to the hospital. The electrocardiogram showed supraventricular tachycardia with a rate of 255 per minute (Fig. 2). Digitalis was given, and the rate was restored to normal within 24 hours. He was discharged after 7 days of observation.

He was seen at intervals in the Outpatient Clinic. He continued to show cyanosis, though his progress was fairly normal. He walked at 15 months, and for a time was quite active. However, he began to fail at about the age of 21 months. Cyanosis increased, the appetite failed, and his ability to exercise became less.

During the period of observation a number of diagnostic possibilities were considered. In early infancy, the cyanosis, the boot-shaped heart, the clear lung fields, and the absence of a murmur led us to believe that he had a tetralogy of Fallot with pulmonary atresia. An x-ray film, at the age of a year, showed an exaggerated boot-shaped heart, the configuration being strongly

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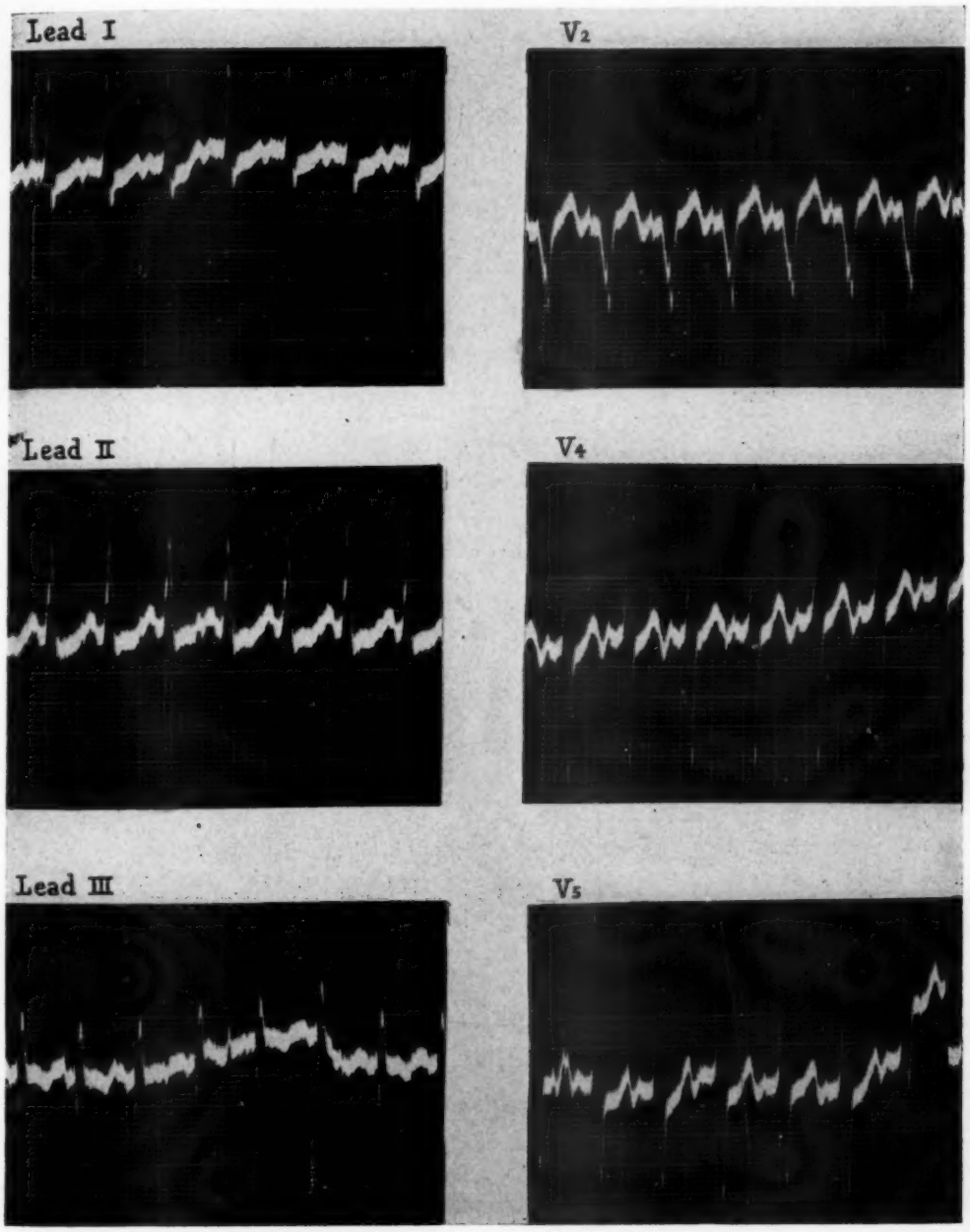


Fig. 1.—Electrocardiogram taken June 2, 1949, showing Wolff-Parkinson-White syndrome. Rate 160. P-R, 0.08 sec. QRS, 0.11 sec.

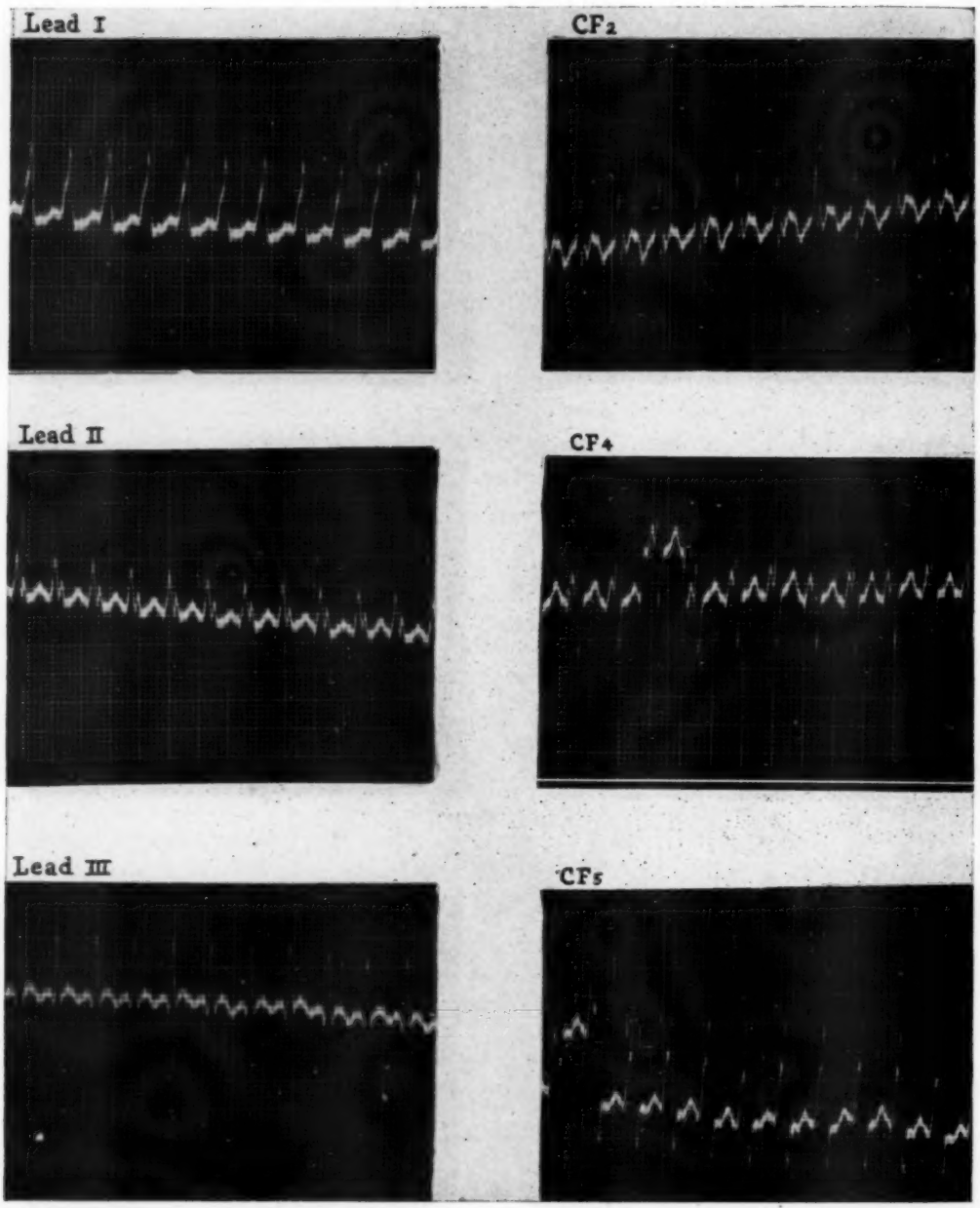


Fig. 2.—Electrocardiogram taken August 27, 1949, showing supraventricular paroxysmal tachycardia. Rate 255 per minute.

suggestive of truncus arteriosus communis (Fig. 3). As time went on, cardiac enlargement was noted, and a Grade 2 blowing systolic murmur was heard at the second left intercostal space. An x-ray film on March 1, 1951, showed the heart to be distinctly larger than at the previous examination, and the silhouette no longer revealed the exaggerated boot, and was somewhat suggestive of pulmonary stenosis with intact ventricular septum (Fig. 4).

Fig. 3.

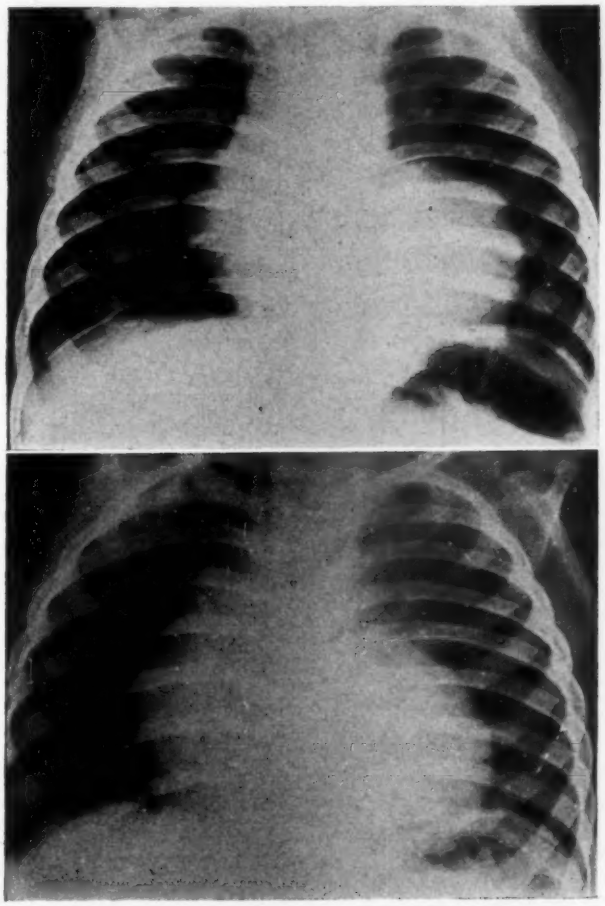


Fig. 4.

Fig. 3.—X-ray of chest taken May 2, 1950.

Fig. 4.—X-ray of chest taken March 1, 1951.

An angiocardiogram at this time was interpreted as showing pulmonary stenosis, a right-to-left shunt between the auricles, and delayed emptying of the right ventricle. The findings were compatible with pulmonary stenosis with intact ventricular septum and open foramen ovale. The child continued to go downhill, and came to operation on May 9, 1951. The surgeon (W. R.) opened the pericardium, and found that the pulmonary artery was small, as was the region of the valve. There was dilatation proximal to the infundibular portion of the right ventricle. It was then thought that he had a tetralogy of Fallot, and an aortic-pulmonary anastomosis was done. On the day after operation, the breathing became grunting in character, his color was ashen, and râles were heard throughout the chest. Death occurred 48 hours after surgery.

Post-mortem Examination.—(Figs. 5 to 7.) Aside from the findings in the heart, the pathologic diagnosis was: (1) acute pulmonary edema, (2) marked chronic passive hyperemia of the liver with central necrosis, (3) aorticopulmonary anastomosis with recent thrombus at site, (4) multiple pulmonary thrombi, (5) focal atelectasis, and (6) cyanosis.

Heart: The heart was enlarged, mostly in its transverse diameter and weighed 90 grams fixed. The apex-base axis pointed toward the left. The apex was formed by the left ventricle.

Fig. 5.

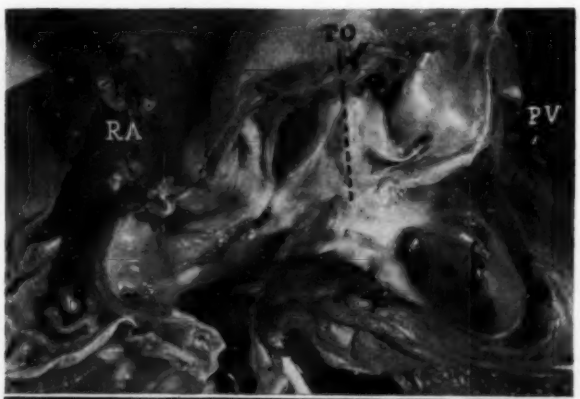


Fig. 6.

Fig. 7.

Fig. 5.—Right atrial and proximal right ventricular view of heart. *RA*, Right atrium. *TO*, Tricuspid orifice without valve. *PV*, Proximal right ventricular chamber.

Fig. 6.—Distal right ventricular view of heart. *PV*, Proximal right ventricular chamber. *TV*, Tricuspid valve. *DV*, Distal right ventricular chamber.

Fig. 7.—Left ventricular view of heart.

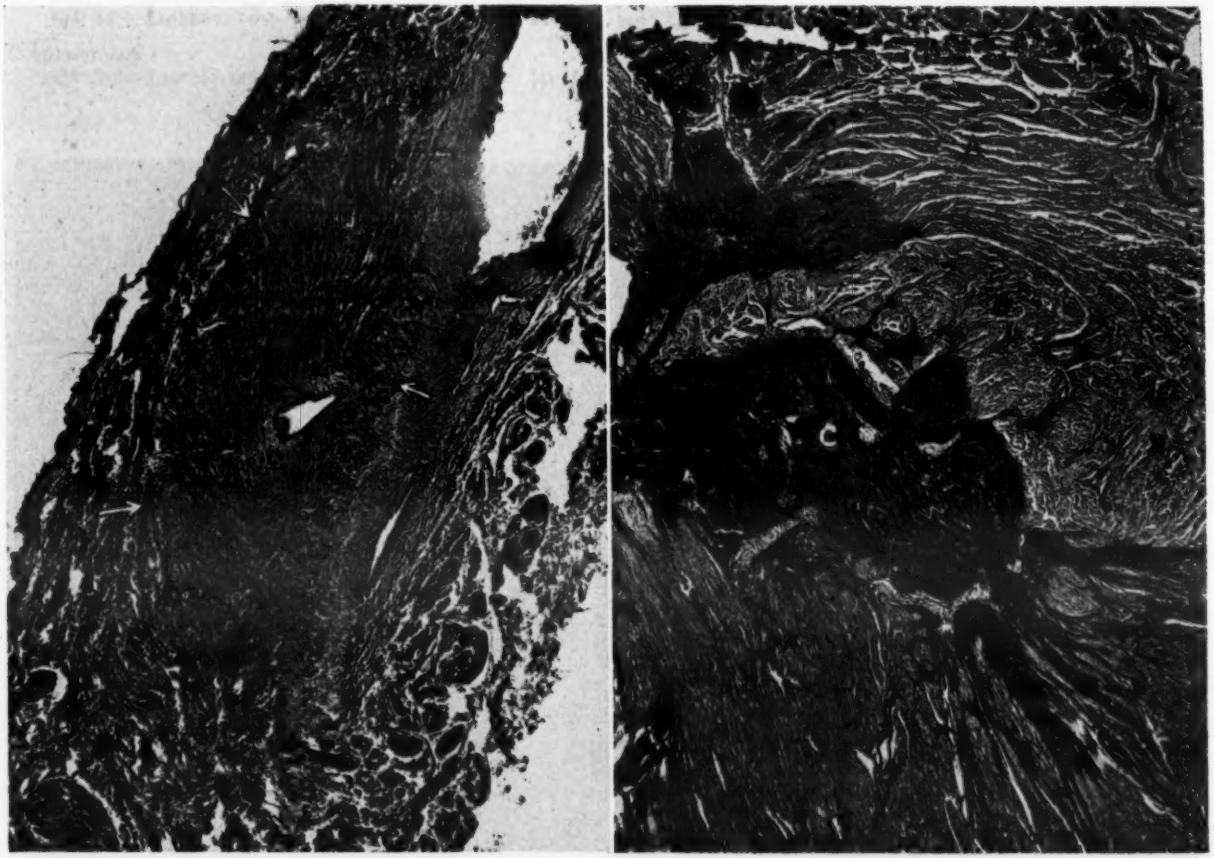


Fig. 8. Fig. 9.

Fig. 8.—The SA node. Arrows point to node. Hematoxylin-eosin stain. (×50; reduced 1/3.)

Fig. 9.—The distal part of AV node and proximal part of penetrating portion of bundle of His. *N*, AV node. *B*, Bundle of His. *A*, Atrial musculature. *V*, Ventricular musculature. *C*, Central fibrous body. Van Gieson stain. (×50; reduced 1/3.)

Fig. 10.

Fig. 11.

Fig. 10.—Penetrating portion of bundle of His. *B*, Bundle of His. *A*, Atrium. *V*, Ventricle. Van Gieson stain. (×50; reduced 1/3.)

Fig. 11.—Proximal part of branching portion of bundle of His. Van Gieson stain. *B*, Bundle of His. *A*, Atrium. *V*, Ventricle. (×50; reduced 1/3.)

From the base two vessels emerged, a larger posterior and to the right, and a smaller anterior and to the left. The anterior descending coronary artery coursed over the middle of the anterior wall of the heart. The right atrioventricular groove was very shallow, but wide.

The right atrium was considerably enlarged, and its wall measured 0.1 to 0.3 cm. in thickness. The superior and inferior venae cavae and coronary sinus entered this chamber in a normal manner. The Eustachian valve was somewhat fenestrated. The Thebesian valve was absent. Along the linea terminalis there was a fenestrated valvelike fold of endocardium. This continued on, as a low ridge, along the upper and proximal margins of the limbus. As it curved along the lower margin of the fossa ovalis, it presented itself as an irregular, fenestrated flat fold lying on the atrial wall which sent strands to the septum primum in the fossa, and finally anchored on the limbus adjacent to the Eustachian valve. The limbus presented a very wide arc, measuring 2 cm. in diameter, and there was a patent foramen ovale measuring 1 cm. in diameter. The right atrial appendage was considerably enlarged.

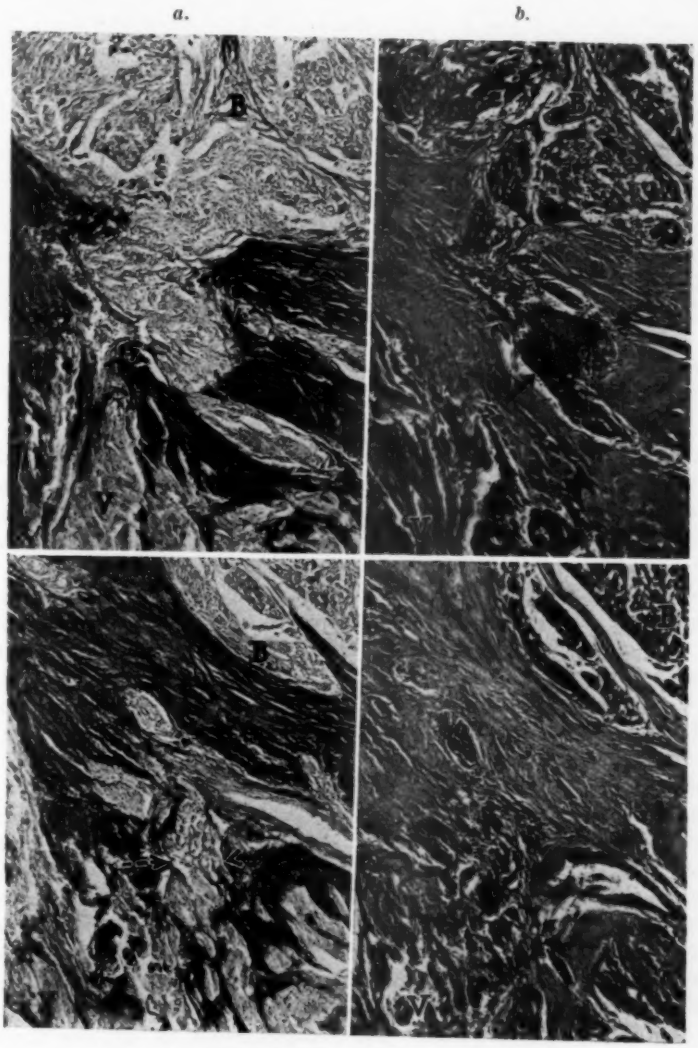


Fig. 12.—Communication between penetrating portion of bundle of His and ventricular musculature. (*a*, *c*) Van Gieson stain. (*b*, *d*) Hematoxylin-eosin stain. *B*, Bundle of His. *V*, Ventricular musculature. Arrows point to communication of bundle and ventricular musculature in successive sections. (×108; reduced 1/3.)

Corresponding to the externally noted right atrioventricular (AV) groove, a right atrioventricular orifice was present, measuring 4 cm. in circumference. There was, however, no valve present at this orifice, and its endocardial lining was smooth. Gross observation of the wall demarcating the right AV orifice, adjacent to the coronary sinus, suggested complete continuity of muscle between right atrium and ventricle.

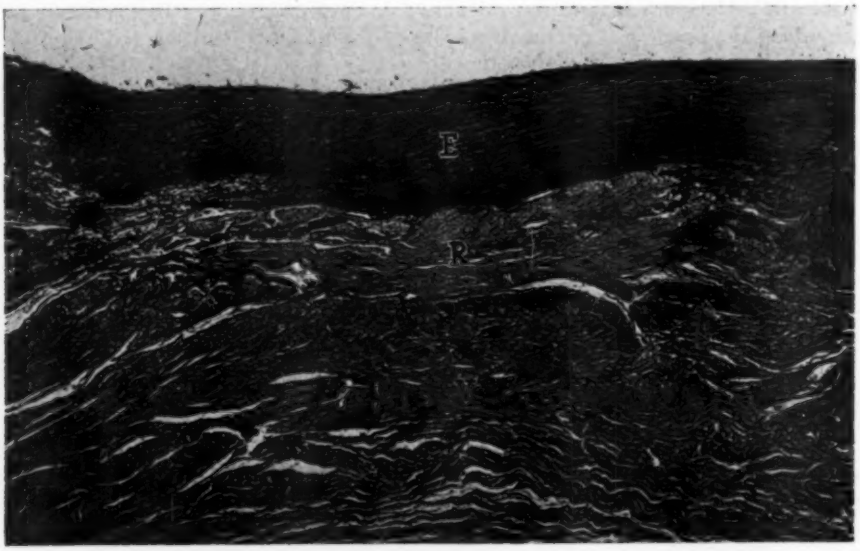


Fig. 13.—Right bundle branch encased in markedly thickened endocardium. *R*, Right bundle branch. *V*, Ventricular musculature. *E*, Endocardium. Van Gieson stain. (×50; reduced ⅓.)

The right ventricle was divided into two chambers, separated by a tricuspid valve. The proximal was the larger chamber. Its parietal wall was very thin, and close to the acute margin presented an aneurysmal dilatation measuring 2 cm. in diameter. The inferior and apical walls measured up to 3 mm. in thickness. The entire endocardial lining of this chamber was whitened and thickened. The right aspect of the interventricular septum in the region of the sinus was outpouched to the left. It presented several arc-shaped clefts. The "pars membranacea" appeared to be muscular. The tricuspid valve was found at a level corresponding to the distal limits of the normal sinus of the right ventricle. Its base was attached to the crista supraventricularis. It guarded an orifice measuring 3.4 cm. in circumference. It consisted of a sheet of thin, lacelike material, whose component three leaflets could barely be delineated. An anterolateral portion was connected to a minute anterolateral papillary muscle, while the other leaflets were attached by chordae to the ventricular wall.

The distal right ventricular chamber, which corresponded to the conus, was a small chamber with a wall measuring 0.1 cm. in thickness. The crista supraventricularis was normal in contour. The right aspect of the interventricular septum in the region of the conus was normal in topography. The pulmonary artery arose from this chamber. Its orifice measured 2.2 cm. in circumference. Its valve consisted of two cusps. The pulmonary artery was small in caliber and gave off proportionately small right and left branches. The ductus arteriosus was closed.

The left atrium was as large as the right, and its wall measured 0.1 to 0.2 cm. in thickness. It was slightly divided into two parts, by two ridges adjacent to the mouths of the left and right pulmonary veins, respectively. The left auricle (atrial appendage) was bizarre in shape and poorly demarcated from the atrium itself. The configuration of the left side of the atrial septum was normal.

The mitral orifice measured 5.3 cm. in circumference. Its valve was large, but normal in structure. The left ventricular chamber was large, and its wall measured 1 cm. in greatest thick-

ness and 0.5 cm. at the apex. The ventricular septum was intact. Its left ventricular surface at the base of the aorta presented a depression in the region of the muscular "pars membranacea." To the left of this, a muscular ridge was noted which extended along the base of the inferior leaflet of the mitral valve. From this chamber emerged the aorta. Its orifice measured 3.2 cm. in circumference. The coronary ostia were normal. The coronary arterial and venous distribution appeared to be normal, but they were not dissected because of the histologic study of the AV orifices. The brachiocephalic vessels were given off normally. A Potts-Smith-Gibson anastomosis joined the left pulmonary artery to the aorta.

Dissection of the atrial musculature was not undertaken since serial sections were to be done. However, gross inspection revealed a normal interatrial band, with right and left anterior and posterior crests.

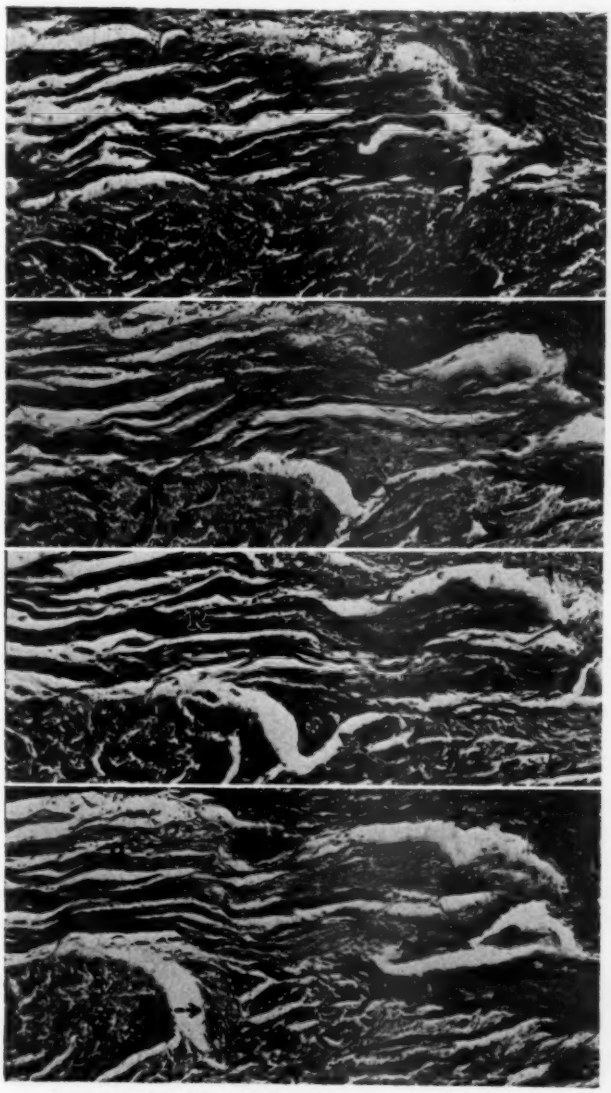


Fig. 14.—Communication between beginning of right bundle branch and ventricular septal myocardium. (*a, c*) Hematoxylin-eosin stain. (*b, d*) Van Gieson stain. *R*, Right bundle branch. *V*, Ventricular musculature. Arrows point to communication between right bundle branch and ventricular musculature in successive sections. (×108; reduced 1/3.)

Pathologic Diagnosis.—Ebstein's disease with (1) pulmonary hypoplasia; (2) patent foramen ovale; (3) hypertrophy of the heart (left ventricle, both atria); (4) aneurysmal dilatation of the right ventricle (proximal chamber); (5) bicuspid pulmonic valve; (6) abnormal endocardial formations of the right and left atria; (7) Potts-Smith-Gibson anastomosis; (8) fibroelastosis of the proximal right ventricular chamber.

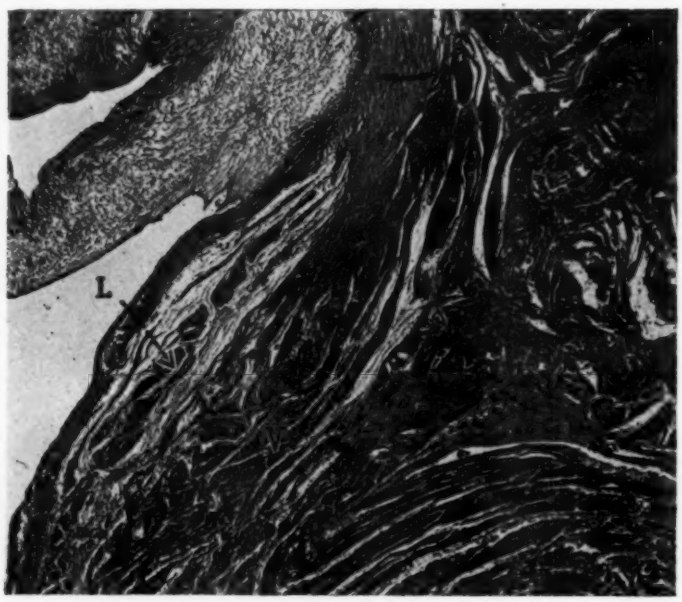


Fig. 15.—Left bundle branch. *L*, Left bundle branch. *V*, Ventricular musculature. Hematoxylin-eosin stain. (×50; reduced 1/3.)

HISTOPATHOLOGIC STUDY OF POSSIBLE CONDUCTION PATHWAYS

A study was undertaken of the regions of the SA and AV nodes, and the AV bundle and bundle branches, in addition to a complete study of the contiguous musculature of both right and left atrioventricular orifices in the formalin-fixed heart.

Blocks for study were taken as follows. (1) The region of the sulcus terminalis and adjacent superior vena cava and right atrium was taken in one block. This contained the SA node. (2) The entire rims of the right and left AV orifices and adjacent atrial musculature up to the Eustachian valve and ventricular musculature up to the base of the right anterolateral papillary muscle were divided into nine blocks. Serial sections were cut at 12-micron thickness through the ten blocks so obtained. Alternate sections were stained with hematoxylin-eosin and Van Gieson stains. A total of 12,083 sections were thus obtained, with a loss of 34 sections.

1. *The SA and AV Nodes, AV Bundle, and Bundle Branches.*—The SA node was normal in architecture and presented no pathologic change (Fig. 8). The AV node originated from the atrial musculature in the usual manner (Fig. 9). It gradually became the penetrating portion of the bundle of His which, however, maintained a connection with the atrium in the beginning of its course

(Figs. 10, 11). Both the node and penetrating portion of the bundle sent wandering fasciculi into the central fibrous body. Only one fasciculus, of 2 to 4 fiber size, originating from the beginning of the bundle, anastomosed with the ventricular musculature (Fig. 12). The node and penetrating portion of the bundle showed no histopathologic change. The branching portion of the bundle was distinctly flattened in contour but showed no other change. It gave off no fasciculi to the upper part of the septum. The right bundle branch arose early from the bundle. It divided itself into several fasciculi which penetrated the dense fibrous endocardium of the right side of the septum, to join again to form

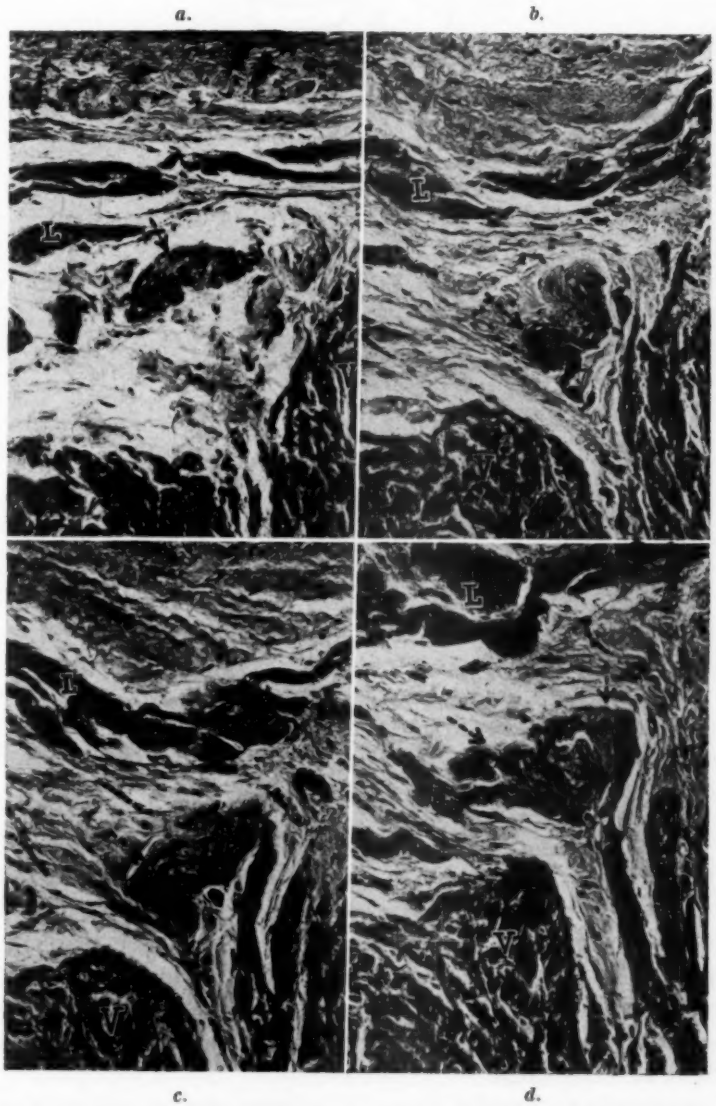


Fig. 16.—Communication between upper part of left bundle branch and ventricular musculature. (*a* to *d*) *L*, Left bundle branch. *V*, Ventricular musculature. Arrows point to communication between left bundle branch and ventricular musculature. Hematoxylin-eosin stain. (×150; reduced 1/3.)

one bundle branch (Fig. 13). This descended without interruption through the dense endocardium of the right septal wall, to fuse with the myocardium in the region of the anterolateral papillary muscle. High on the septum, at the point where its component fasciculi became one bundle branch, it gave off a short fasciculus of 6 to 8 fibers thick, which terminated (anastomosed) rapidly into the myocardium of the right ventricular septal wall (Fig. 14). The remainder of

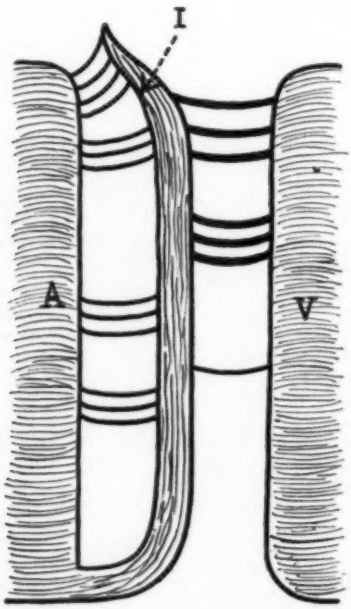


Fig. 17.—Diagrammatic sketch of atrioventricular communications of parietal wall of right side of heart. *A*, Atrial musculature. *V*, Ventricular musculature. *I*, Intermediate bundle.

the right bundle branch gave off no more branches to the septum until its termination. The left bundle branch arose in a normal fashion from the bundle and gave off its normal anterior and posterior radiations (Fig. 15). The lowermost portions were not followed to the papillary muscles. About 5 cm. from its origin, the left bundle branch gave off a 2 to 3 fiber fasciculus to the left side of the ventricular septum (Fig. 16).

2. *The Right Atrioventricular Orifice.*—In the connective tissue of the atrioventricular groove, an intermediary muscle bundle was noted (Figs. 17, 18). This arose from the connective tissue of the right AV ring on its parietal aspect, a short distance from the central fibrous body. It coursed through the AV ring along the parietal wall adjacent to the endocardium, and at the level of the right circumflex coronary artery. In the region of the acute margin of the heart, and close to the inferior termination of the right atrial appendage, it fused completely with the right anterior crest.

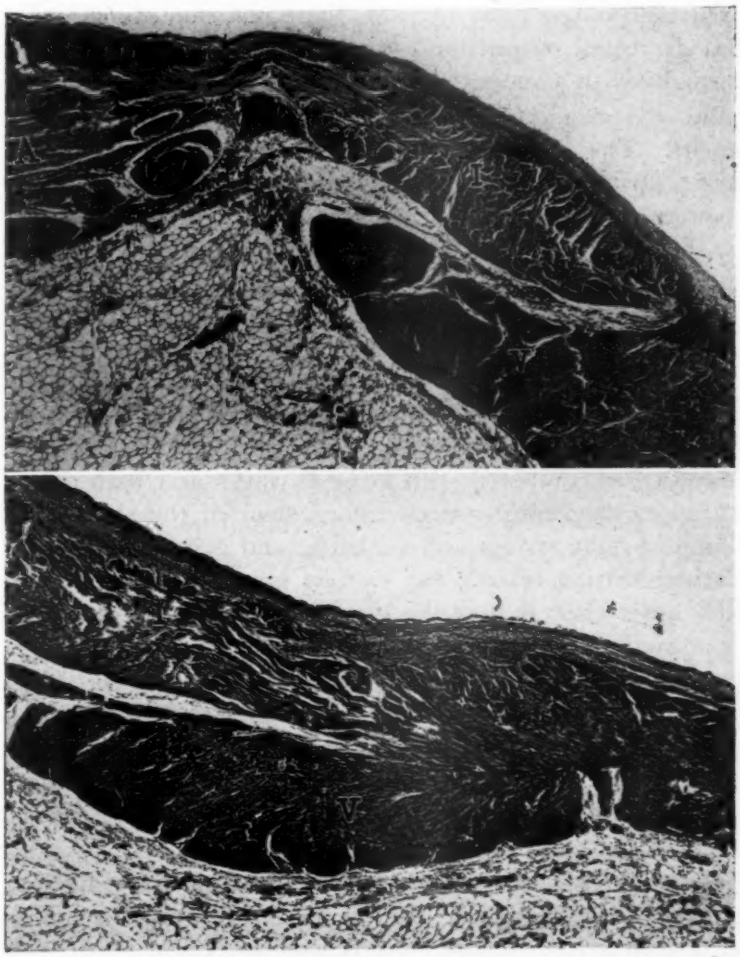
This intermediary bundle gave off numerous fasciculi to the right atrial appendage and the parietal wall of the right ventricle (Figs. 17, 18). The fasciculi going to the atrium were more numerous than those to the ventricle, but

the latter were larger. These fasciculi were especially numerous in the superior half of the parietal wall. It is thus apparent that the atrium and ventricle had an interrupted muscular continuity for a distance of about 2 cm.

The apparent muscular continuity, seen grossly along the acute margin of the right ventricle, histologically proved to be nonexistent, the atrial and ventricular musculature being separated by a thin, connective tissue wall.

3. *Left Atrioventricular Orifice.*—The atrioventricular ring was histologically normal, and the atrial and ventricular musculatures were completely separated throughout their extent.

a.



b.

Fig. 18.—Communication between intermediate bundle and atrial and ventricular musculatures. (*a*) Communication between intermediate bundle and atrial myocardium. Van Gieson stain. (*b*) Communication between intermediate bundle and ventricular myocardium. *A*, Atrial musculature. *V*, Ventricular musculature. *I*, Intermediate bundle. Hematoxylin-eosin stain. (×50; reduced 1/3.)

DISCUSSION

The clinical and pathological characteristics of Ebstein's anomaly have been repeatedly reviewed.[1-15] In this anomaly, there is displacement of the tricuspid valve downward into the right ventricle. This divides this chamber into a thin-walled proximal and thicker distal portion. The new tricuspid orifice, as in our case, may be at the line of junction of the sinus and conus. The anterolateral leaflet is partly attached to the annulus, while the posterior is not attached at all. The septal leaflet may or may not be attached. All leaflets may be thickened and their identity indistinguishable. The new tricuspid orifice may be small or large, and may be normal functionally, or the seat of an insufficiency or, less commonly, stenosis. There is almost always an associated patent foramen ovale. The Eustachian and Thebesian valves may be prominent.

From the physiologic point of view, there is a small functioning right ventricle with a decreased output, and hence decreased pulmonary flow. This is associated usually with a venoarterial shunt in the atrial region.

Clinically, dyspnea is the outstanding symptom, and cyanosis is almost always present. The presence of cyanosis is apparently correlated with the presence of an atrial septal defect. Palpitation, precordial pain, and syncope are less common symptoms. On physical examination, the heart is always enlarged, with the presence of variable murmurs. A rough systolic murmur, heard best at the left border of the sternum, is usual. In a smaller number of cases, there is a diastolic murmur in this area, and rarely a continuous murmur. A gallop rhythm is often present, with reduplication of one or both heart sounds. X-ray findings often present an enlarged heart, with a bulging left border forming one big elevated convexity, together with normal or faint hilar markings. The electrocardiogram is always abnormal. As a rule, there is a right bundle branch block, in some cases combined with large P waves and with delayed AV conduction. Angiocardiography reveals enlargement of the right atrium, delayed emptying time of right atrium and ventricle, and poor filling of the pulmonary artery. Catheterization reveals the systolic pressure in the pulmonary artery to be slightly lower than that of the right atrium, but the pressure in the right ventricle is normal.

Our case showed the general characteristics of those found in the literature. The preoperative diagnosis of pulmonary stenosis with atrial septal defect might have been modified had catheterization been done. As pointed out by Gøtzsche and Falholt,[15] Ebstein's anomaly can be differentiated from Morgagni's syndrome by the demonstration of the absence of increased pressure in the right ventricle in the former.

The findings in this case of a short P-R interval with prolonged QRS—the Wolff-Parkinson-White syndrome—or the pre-excitation syndrome, or accelerated conduction, are of great interest. As is well known, this arrhythmia can be found in normal hearts and in acquired heart disease. This has been found in Ebstein's anomaly by Sodi-Pallares,[16] and in Roger's disease by Segers and associates.[17]

The theories which have been propounded to explain this arrhythmia are protean and have been repeatedly reviewed.[17-25] Prinzmetal and his associates[25]

have grouped them into (1) those that postulate an accessory bundle outside the conducting system connecting atrium and ventricle, and (2) those that consider the arrhythmia to be in the abnormal structure or function of the conduction system itself. Anatomic studies, however, to lend substance to the various theories, have been scant. Wood and associates[26] found three muscle communications between the right atrium and ventricle in a case of Wolff-Parkinson-White syndrome. Öhnell[19] found a muscle connection between the left atrium and ventricle in another case. Deerhake and associates[27] also found a right-sided communication. In other cases, however, Holzmann,[28] Öhnell,[29] and Langendorf and associates[23] did not find such communications.

Mahaim and Bogdanovic,[21] Prinzmetal and associates,[25] and Segers and associates[17] have examined parts of the conduction system in cases with Wolff-Parkinson-White syndrome. Mahaim and Bogdanovic found inflammation of the left bundle branch and around the right bundle branch. There were no paraspecific connections between the AV node and bundle and the septum. Prinzmetal and associates and Langendorf and associates found pathologic changes in the AV node. Segers and co-workers found a connection between the AV node and the septum.

It is self evident that anatomic evidence in favor of any of the theories cannot safely be offered unless the entire conduction system, as well as the entire AV rings, are studied by serial sections. This was done in our case. This study showed that SA and AV nodes, the bundle of His, and the left bundle branch were normal in contour and showed no acquired pathologic changes. The right bundle branch, however, was encased by the markedly thickened endocardium, but showed no internal change, and no interruption in continuity. Small communications were found between the beginning of the penetrating parts of the bundle of His, the left branch about 1 cm. from its origin, and the right branch in the uppermost part of the septum, and the ventricular myocardium. Multiple large communications were found between the right atrial appendage and the right ventricle, through a large intermediary bundle. No such communications were present on the left side.

These findings can be evaluated only with the reference to the atrioventricular communications in the normal heart. These have recently been studied by Lev and Lerner[30] in twenty-seven fetal and neonatal hearts by serial sections. This study showed that normally there are no atrioventricular communications outside the conduction system. Connections, of the type described by Mahaim and his associates,[31-35] are frequently present in fetal hearts between the terminal portion of the AV node, the beginning of the penetrating part of the bundle of His, and the beginning of the left branch and the ventricular septum. Such communications were not found between the right bundle branch and the septum.

From this, it becomes clear that the abnormal findings in our present case were: (1) the large right AV communication outside the "conduction system," (2) the small communication of the right branch and the right side of the septum, and (3) the encasement of the right branch in dense, fibroelastic tissue. The anatomic evidence in our case, therefore, supports the theory which postulates an accessory atrioventricular communication outside the conduction system, as involved in the genesis of the Wolff-Parkinson-White syndrome. To a lesser

extent, it is in keeping with the theory which postulates a right bundle branch paraseptal communication, or secondary pathologic change in the right bundle branch. This, of course, does not mean that all cases of the Wolff-Parkinson-White syndrome have this anatomic base. Insufficient cases have been examined histologically to make all inclusive statements. The experimental work of Prinzmetal and associates,[25] Sodi-Pallares and associates,[36] and Butterworth and Poindexter[37] suggests that there are many anatomic and function patterns responsible for Wolff-Parkinson-White syndrome.

SUMMARY

1. A case of Ebstein's disease associated with the Wolff-Parkinson-White syndrome is presented.

2. Histopathologic studies of the entire conduction system and of the entire right and left atrioventricular rims revealed: (a) a large AV communication in the parietal wall of the right ventricle, (b) a small, high communication between the right bundle branch and the ventricle, and (c) a right bundle branch encased in fibroelastic tissue. Any one of these abnormalities may be related to the Wolff-Parkinson-White syndrome.

SUMMARIO IN INTERLINGUA

1. Es presentate un caso de morbo de Ebstein associate con syndrome de Wolff-Parkinson-White.

2. Studios histopathologic del integre systema de conduction e del integre dextere e sinistre margines atrioventricular revelava le presentia de (a) un grande communication atrioventricular in le pariete del ventriculo dextere, (b) un restringite alte communication inter le branca dextere e le ventriculo, e (c) un branca dextere incassate in texito fibroelastic. Cata un de iste anormalitates pote esser relationate al syndrome de Wolff-Parkinson-White.

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A COMPARISON OF RAUWOLFIA SERPENTINA COMPOUNDS, CRUDE ROOT, ALSEROXYLON DERIVATIVE, AND SINGLE ALKALOID, IN THE TREATMENT OF HYPERTENSION

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RAUWOLFIA serpentina is a valuable addition to the medical armamentarium in the treatment of patients with arterial hypertension because of its ease of administration and insignificant side effects. Attempts have been made to aid the medical practitioner in selecting patients suitable for chronic oral therapy using the various available Rauwolfia compounds.[1-3] The choice of proper treatment is becoming more difficult because of the numerous derivatives of Rauwolfia available. Among these are the crude root, Raudixin*; the alseroxylon compound, Rauwiloid†; and the various single alkaloids, including reserpine.‡

It is the purpose of this paper to present preliminary observations on the continued oral administration of these Rauwolfia serpentina preparations in arterial hypertension and to compare their hypotensive effects.

METHODS AND MATERIALS

These drugs were given to forty-seven patients from the wards of the University of Wisconsin Hospitals or observed in the Hypertension Clinic. There were twenty-two men and twenty-five women with mild to severe arterial hypertension. Their ages ranged from 20 to 68 years. These patients were observed for from two to fourteen months as outpatients. Pretreatment studies included a complete history and physical examination, complete blood count, urinalysis, electrocardiogram, ophthalmoscopic examination, renal function studies (PSP, NPN, concentration test), chest x-ray and, where indicated, pyelography and Regitine tests.

The drugs employed in this study included Raudixin (Squibb), reserpine (Squibb), Rauwiloid (Riker), and Serpasil (reserpine-Ciba).

Thirty-two of the forty-seven patients (68 per cent) had diastolic blood pressures of 120 or greater and the remaining seventeen (32 per cent) had diastolic levels between 110 and 120 mm. Hg. The mean arterial blood pressure (MABP) was calculated by adding one-third of the pulse pressure to the diastolic pressure. The calculated MABP ranged from 130 mm. Hg to 190 mm. Hg.

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*Raudixin supplied by E. R. Squibb & Sons, New York, N.Y.

†Rauwiloid supplied by Riker Laboratories, Inc., Los Angeles, Calif.

‡Reserpine supplied as Serpasil by Ciba Pharmaceutical Products, Inc., Summit, N.J.; and reserpine (2012X) by E. R. Squibb & Sons, New York, N.Y.

Six of the patients had previously been treated by thoracolumbar sympathectomy. Congestive failure was being treated with digitalis in seven other patients. Forty-two of the patients were found to have Grade 1-2 Keith-Wagener-Barker eye ground changes, three Grade 3, and two Grade 4. Three patients had had previous cerebral vascular accidents. Two patients had nonprotein nitrogen levels greater than 40 mg./100 c.c. whereas many of the others showed mild to moderate renal impairment as measured by maximum urinary concentration and phenolsulfonphthalein excretion.

After complete evaluations the patients were arbitrarily started on one of the four following regimens: Raudixin, 200 mg./day; reserpine (Squibb), 0.2 mg./day; Rauwiloid, 8 mg./day; or Serpasil, 1.0 mg./day. They were given clinic appointments at four to six week intervals for follow-up evaluation. With each clinic visit an interim history, postural blood pressure determinations, and pertinent physical examination and laboratory tests were performed. Dosage levels were decreased only after drug effect was noted, manifested by nasal stuffiness, bradycardia with a rate of 60 or less, excessive sedation or decrease of the blood pressure to normotensive levels (140/90 mm. Hg or below). It is on the basis of these repeated examinations that the decision was made as to which patients required additional therapy with the more potent hypotensive agents as outlined by Wilkins.[4]

Control blood pressures were determined by averaging all pretreatment pressures recorded, either during the patient's hospital stay or during his outpatient visits. The treatment blood pressures are averages of the patient's pressures taken on his most recent visit to the clinic.

Five of the forty-seven patients were in the premalignant or malignant phase of hypertensive disease. Generally patients with severe hypertensive cardiovascular disease (Smithwick and Thompson, Groups 3 and 4)[5] were hospitalized and started on a Rauwolfia compound while being treated simultaneously with hydralazine, hexamethonium, or veratrum viride. Intravenous Serpasil was also used in doses of 1.0 to 4.0 mg. as a single injection to decrease the blood pressure before starting the patients on chronic oral therapy. Patients treated with combination therapy from the onset of their treatment are not included in this study. Included, however, is the blood pressure response of six patients while receiving Rauwolfia who later required combination therapy.

RESULTS

The blood pressure response of the patients receiving the four medications is shown in Tables I to IV and the entire group summarized in Table V. The average pretreatment blood pressure for the forty-seven patients was 205/123 mm. Hg with a MABP of 150 mm. Hg. Following an average of six months of therapy, the average pressure was 152/97 mm. Hg with a MABP of 115 mm. Hg, a reduction of 35 mm. Hg. The blood pressure decrease in each group is statistically significant ($p < 0.01$). Forty-one patients (87 per cent) had a decrease in MABP of 20 mm. Hg or more. Twenty-nine patients (61 per cent) had a MABP following therapy of 117 mm. Hg (150/100) or below and in twelve of these the blood pressure fell to normotensive levels (140/90 or below). Six

TABLE I. BLOOD PRESSURE RESPONSE TO RESERPINE (SQUIBB) IN 8 PATIENTS

PATIENT	AGE	SEX	DIAGNOSIS	CONTROL BP	CONTROL MABP	TREATMENT BP	TREATMENT MABP	MABP DECREASE	TREATMENT PERIOD (MO.)	DOSE MG./DAY	SIDE EFFECTS	COMPLICATION OF DISEASE
1. P.B.	66	M	HASCVD	240/128	165	190/110	137	28	5	0.2	None	CF
2. R.F.	34	M	HVD	190/135	153	164/110	128	25	4	0.2	NS	None
3. A.F.	66	M	HASCVD	210/130	157	170/86	114	43	3	0.2	NS, Mild dizziness	CVA, CF
4. C.P.*	37	M	HVD	210/140	163	180/130	147	16	2	0.2	NS	KWB—Grade 3
5. E.P.	48	F	HVD	190/120	143	140/100	113	30	5	0.2	MS	None
6. C.R.	40	M	HVD	180/120	140	160/110	127	13	5	0.2	MS	None
7. W.S.	39	M	HVD	185/110	135	140/90	107	28	2	0.2	None	None
8. H.W.	42	F	HVD	210/110	143	160/100	120	23	3	0.2	None	None
Av.	46.5			202/124	150	163/105	124	26	3.6	0.2		

Key:

M = Male
F = Female
BP = Blood pressure
MABP = Mean arterial blood pressure
NS = Nasal stuffiness
*Another hypotensive drug added

HASCVD = Hypertensive arteriosclerotic cardiovascular disease
HVD = Hypertensive vascular disease
HCVD = Hypertensive cardiovascular disease

AV = Average
–S = Sympathectomy
CF = Congestive failure
CVA = Cerebral vascular accident
KWB = Keith-Wagener-Barker classification

CP = Chronic pyelonephritis
NR = Nitrogen retention
MS = Moderate sedation
DL = Decreased libido
NB = Nose bleed
PL = Painful legs

TABLE II. BLOOD PRESSURE RESPONSE TO RAUDIXIN IN 18 PATIENTS

PATIENT	AGE	SEX	DIAGNOSIS	CONTROL BP	CONTROL MABP	TREATMENT BP	TREATMENT MABP	MABP DECREASE	TREATMENT PERIOD (MO.)	DOSE MG./DAY	SIDE EFFECTS	COMPLICATION OF DISEASE
1. A.S.	48	F	HVD	220/120	153	180/110	133	20	10	200	None	None
2. E.D.	40	M	HCVD–S	166/124	138	138/105	116	22	4	200	NS, MS	None
3. A.F.	68	M	HASCVD	210/130	157	142/90	107	50	7	200	NS, MS, Dizziness	CF, CVA
4. R.H.	61	M	HASCVD	190/110	137	138/80	99	38	5	200	NS, NB, PL	CF
5. E.K.	51	F	HVD	190/110	137	150/100	113	24	5	200	NS	None
6. E.M.	52	M	HCVD	220/130	160	140/104	116	46	9	150	NS	CF
7. C.P.*	37	M	HVD	210/140	163	170/126	141	22	5	300	NS	KWB—Grade 3
8. O.R.	40	M	HVD	180/120	140	150/100	113	27	5	200	MS	None
9. G.S.	68	F	HASCVD	270/140	183	210/90	130	53	4	200	NS	CF
10. W.S.	39	M	HVD	185/110	135	154/92	115	20	3	200	NS	None
11. M.S.	38	F	HVD	215/125	155	160/110	127	28	5	200	NS	None
12. F.S.	50	M	HCVD	240/140	173	150/70	97	76	6	200	PL, NS	CF, KWB—Grade 3
13. I.W.	39	F	HVD	170/110	130	136/100	112	18	4	200	NS	None
14. C.S.	54	M	HVD	230/130	163	150/90	110	53	5	200	NS, MS	None
15. H.D.*	42	F	HCVD–S	200/130	153	175/120	138	15	4	200	NS	None
16. C.B.	52	F	HASCVD	185/110	135	140/80	100	35	4	100	NS, MS	None
17. F.M.	48	F	HVD	220/120	153	155/90	112	41	3	200	NS	None
18. E.P.	48	F	HVD	190/120	143	120/80	93	50	5	200	NS	None
Av.	48.6			205/123	150	153/96	115	35	5.2	±200		

For key see Table I.

TABLE III. BLOOD PRESSURE RESPONSE TO RAUWILOID IN 14 PATIENTS

PATIENT	AGE	SEX	DIAGNOSIS	CONTROL BP	CONTROL MABP	TREATMENT BP	TREATMENT MABP	MABP DECREASE	TREATMENT PERIOD (MO.)	DOSE MG./DAY	SIDE EFFECTS	COMPLICATION OF DISEASE
1. H.B.	40	F	HCVD	220/125	157	150/90	110	47	6	8.0	NS	None
2. J.E.	47	M	HVD	190/115	140	144/92	109	31	5	6.0	NS, DL	None
3. J.F.	20	F	HCVD–S	190/110	143	130/98	109	34	13	6.0	NS	None
4. C.G.	57	M	HVD	200/115	143	180/110	133	10	4	4.0	NS	None
5. D.H.	34	F	HVD	180/110	133	122/86	98	35	7	2.0	Dizziness	None
6. R.J.	45	M	HVD	190/120	143	120/80	93	50	9	3.0	MS	None
7. E.K.	40	F	HVD	210/110	143	170/100	120	23	14	4.0	NS	None
8. D.K.	42	F	HCVD–S	180/110	133	90/60	70	63	13	2.0	NS	None
9. A.K.	51	F	HCVD	200/130	153	135/100	112	41	10	4.0	NS	None
10. A.K.*	42	F	HCVD–S	220/140	167	165/120	135	32	11	8.0	None	None
11. N.L.*	50	M	HCVD	270/150	190	200/110	140	50	4	8.0	NS, MS, Dizziness	KWB—Grade 4 NR
12. H.P.	52	F	HVD	190/120	143	130/96	107	36	10	6.0	NS	None
13. W.S.	63	M	HASCVD	200/120	147	170/120	137	10	4	8.0	None	None
14. R.W.	45	M	HVD	200/120	147	120/80	93	54	8	2.0	None	None
Av.	44.9			203/121	149	145/96	112	37	8.4	5.1		

For key see Table I.

TABLE IV. BLOOD PRESSURE RESPONSE TO SERPASIL IN 7 PATIENTS

PATIENT	AGE	SEX	DIAGNOSIS	CONTROL BP	CONTROL MABP	TREATMENT BP	TREATMENT MABP	MABP DECREASE	TREATMENT PERIOD (MO.)	DOSE MG./DAY	SIDE EFFECTS	COMPLICATION OF DISEASE
1. H.H.	41	M	HCVD–S	185/125	145	115/80	92	53	8	0.75	NS, PL	None
2. A.L.	58	F	HASCVD	230/130	163	156/108	123	40	5	0.50	None	CF
3. F.R.	48	F	HVD	230/130	163	110/80	90	73	8	0.75	NS	None
4. H.W.	42	F	HVD	210/110	143	160/104	122	21	6	1.0	NS	None
5. M.H.	61	F	HASCVD	210/120	150	140/90	107	43	3	1.0	None	None
6. D.J.*	42	F	CP	250/150	183	210/120	150	33	4	1.0	NS	KWB—Grade 4 CVA, NR
7. V.L.	51	F	HASCVD	190/110	137	145/85	105	32	4	1.0	NS, MS	None
Av.	49			215/125	155	148/95	113	42	5.4	0.85		

For key see Table I.

TABLE V. COMPARISON OF BLOOD PRESSURE RESPONSE OF FOUR RAUWOLFIA COMPOUNDS USED IN CHRONIC ORAL THERAPY

DRUG	NO. OF PATIENTS	AV. AGE	AV. CONTROL BP	AV. MABP	TREATMENT BP	TREATMENT AV. MABP	MABP DECREASE	TREATMENT PERIOD (MO.)	AV. DOSE MG./DAY
Reserpine (Squibb)	8	46.5	202/124	150	163/105	124	26 ± 9.2*	3.6	0.2
Rauwiloid	14	44.9	203/121	149	145/96	112	37 ± 15.6*	8.4	5.1
Raudixin	18	48.6	205/123	150	153/96	115	35 ± 16.1*	5.3	±200
Serpasil	7	49	215/125	155	148/95	113	42 ± 14.1*	5.4	0.85
Mean average	47	47.2	205/123	150	152/97	115	35	6.0	

*Statistically significant change ($p < .01$)

of the twelve patients whose pressures fell to normotensive levels had a diastolic pressure of 120 mm. Hg or more during the control period. Six patients had a fall in MABP of 10 to 18 mm. Hg.

Six other patients, five of whom had a fall in MABP of 20 mm. Hg or more with Rauwolfia, required supplemental therapy later with hydralazine or veratrum viride. Two of these patients had previously undergone sympathectomy. The remaining four patients who had been sympathectomized were treated only with Rauwolfia.

Blood pressure reductions with Serpasil in seven patients averaged 42 mm. Hg but the control MABP was 155 mm. Hg, slightly higher than in the remainder of the group. The reduction in MABP was only 26 mm. Hg with reserpine (Squibb), but significantly different ($p < 0.05$) only from those receiving Serpasil. Smaller doses of this compound (0.2 mg.) were used because of a study now in progress in which patients are being alternated with Raudixin, two tablets (100 mg.) twice daily, and reserpine (Squibb), two tablets (0.1 mg.) twice daily. (The 0.05 mg. tablet of reserpine is identical in appearance to the 50 mg. Raudixin tablet.) It would seem from these early observations in hypertensive patients that the blood pressure-lowering effect of the single alkaloid (reserpine) compared with the crude root (Raudixin) more nearly approaches the ratio of 1:750 or 1:500 than the original estimation of 1:1000. Furthermore, in terms of the blood pressure-lowering effect, these observations also suggest that one is able to distinguish between two doses of reserpine (Squibb reserpine, 0.2 mg. and Ciba Serpasil, 0.85 mg.) which differ only by a factor of approximately four. It should be noted, however, that the average duration of treatment with reserpine (Squibb) is 3.6 months, a shorter period of observation than that for the group as a whole (six months) or those patients treated with Raudixin (5.3 months).

The side effects noted in the use of these Rauwolfia compounds were of comparable incidence and severity. All have been of a mild to moderate degree. There was a decrease in heart rate in all patients, unrelated to the degree of blood pressure reduction. Nasal stuffiness was present in thirty-three of the forty-seven patients. Four patients complained of a feeling of "dizziness", three of leg weakness and calf pain, and eight of moderate sedation. One patient complained of decreased sexual desire and another of epistaxis. None of the patients complained of diarrhea. Many of the patients volunteered that they had "never felt better" and stated they had noted a decrease in nervousness and irritability. Some of these patients stated that their friends and relatives had perceived these changes. This "improvement in personality" has previously been described by Wilkins and Judson.[6]

DISCUSSION

Titration of any of the Rauwolfia compounds is difficult. The "end-point" is indistinct and the onset of action and maximum benefit are frequently delayed as contrasted with the veratrum compounds, where an established dose will lower the blood pressure to a similar level on two or more successive days.[7] The patient continues with the established dose until the specific drug effects are present. If the blood pressure still shows no significant moderation, this dose

is continued for another six to eight weeks before starting the patient on combination therapy. This can be done with relative safety, especially in patients showing labile hypertension without significant progression of vascular disease. Frequently this approach has proved efficacious. For example, one patient, P.R., a 48-year-old woman with a blood pressure of 230/130 mm. Hg (MABP = 163) was discharged from the hospital while taking Serpasil 0.25 mg. three times a day. She failed to return until six months later. She had continued taking the medication and was asymptomatic. Her blood pressure was recorded at 110/80 mm. Hg (MABP = 93), a decrease of 70 mm. Hg in her MABP.

Successful therapy with Rauwolfia serpentina depends on two principles, an adequate quantity of medication and prolonged administration. The duration of treatment appears to be most important. We have frequently seen patients who were referred to the Hypertension Clinic because of "medically-resistant hypertension." Many of these had received one of the Rauwolfia preparations for one to two weeks with no decrease in blood pressure. They were, therefore, referred for "more intensive therapy." Often continuation of the same medication for six to eight weeks produced the desired moderation of the pressure. Furthermore, no time is wasted by this practice for, if another medication seems indicated, the Rauwolfia compound serves as an excellent additional agent.[3,8]

It would appear from these observations that there is no significant difference in the hypotensive effect of Raudixin and reserpine (Squibb) ($p < 0.1$), Raudixin and Rauwiloid ($p < 0.07$), or Raudixin and Serpasil ($p < 0.3$). The only significant difference demonstrated is that between reserpine (Squibb) and Serpasil ($p < 0.05$). However, this may be explained on the basis of difference in average dose (0.65 mg.) and length of treatment (1.8 months) in the patients receiving the two drugs.

When comparing blood pressure reduction or side reactions in patients with hypertension, Hughes and associates[2] could find little difference between reserpine (Serpasil) and Rauwiloid. This might support the theory that reserpine is the active blood pressure lowering principle in all Rauwolfia compounds.

The control of side reactions has not been a problem in maintaining adequate dosage levels. Patients were instructed to eliminate the next scheduled dose if the side effects were intolerable and then to continue with the regular dosage schedule. Tolerance to these untoward symptoms developed if the patient continued the medication.

It has been stated that the Rauwolfia compounds are most beneficial in the early labile hypertensive state with diastolic blood pressures less than 120 mm. Hg. In most instances this is true, but not as a hard and fast rule. It has been previously stated[9] that the only method of determining response of any patient to Rauwolfia therapy is adequate and prolonged administration.

SUMMARY AND CONCLUSIONS

1. Observations on the continued use of reserpine (Squibb), Raudixin (Squibb), Rauwiloid (Riker), and Serpasil (reserpine-Ciba) in forty-seven selected patients with arterial hypertension are presented.

2. The average blood pressure reduction was 35 mm. Hg in the MABP. This decrease is statistically significant ($p < 0.01$).

3. Generally there was no significant difference in the blood pressure-lowering effect between these agents.

4. These observations indicate that the blood pressure-lowering effect of the single alkaloid (reserpine, Serpasil) compared with the crude root (Raudixin) more nearly approaches the ratio of 1:750 or 1:500 than the original estimation of 1:1000.

5. These observations also suggest that one is able to distinguish between two doses of reserpine (Squibb reserpine, 0.2 mg., and Ciba Serpasil, 0.85 mg.) which differ only by a factor of about four.

6. The latent period which may precede the therapeutic effect of these compounds makes prolonged administration an important principle in Rauwolfia therapy.

7. Whether or not a patient will respond to Rauwolfia serpentina depends on an adequate therapeutic trial.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Es presentate observationes in re le continue uso de resperpina (Squibb), Raudixina (Squibb), Rauwiloide (Riker) e Serpasil (reserpina Ciba) in quarantasepte seligite patientes con hypertension arterial.

2. Le nivello median del pression sanguinee arterial del patientes individual monstrava un reduction amontante pro le gruppo integre al valor median de 35 mm Hg. Isto es statisticamente significative.

3. In general nulle differentia significative esseva notate inter le effectos hypotensive producite per le varie agentes.

4. Nostre observationes indica que le effectos hypotensive del singule alcaloide (reserpina, Serpasil) se compara con le effectos hypotensive del radice crude (Raudixina) approximativemente secundo le proportion 1 a 750 o 1 a 500 plus tosto que secundo le proportion 1 a 1000 que esseva previemente estimate.

5. Le periodo latente que pote preceder le effecto therapeutic de iste compositos sublinea le importantia de un prolongate curso de administrationes in omne therapia a *Rauwolfia*.

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CLINICAL RESULTS WITH THE USE OF ROXINIL (AN EXTRACT OF RAUWOLFIA SERPENTINA) IN THE TREATMENT OF HYPERTENSION

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PRELIMINARY observations have indicated that the whole root of Rauwolfia serpentina and some of its extracts are effective therapeutic agents[1-4] for the treatment of hypertension. However, these agents are only moderately potent in their ability to reduce the blood pressure. Therefore, it is only natural that continued effort should be made to isolate pure alkaloids or to prepare extracts containing multiple alkaloids which will be more consistently effective in the treatment of patients with hypertension, particularly in patients with severe forms of the disease. The current report is based on results obtained with an extract which contains multiple alkaloids, but in different proportions than in preparations currently available. This extract is an attempt to combine the potent and immediate depressor effects of the serpentine-type alkaloids with the hypnotic action of the reserpine-like materials. In contrast to reserpine, laboratory observations indicate that Roxinil retains some adrenergic blocking action of the ajmoline and serpentine group of alkaloids.[5]

METHODS AND MATERIALS

A total of forty cases with hypertensive vascular disease have been investigated in this study. The patients were treated on an outpatient basis, either as private patients or in the Cardiac Clinic of the Jefferson Davis Hospital or the Veterans Administration Hospital. They were observed for one month or more before treatment was started. The control blood pressures as recorded in the current report are the averages of all pressures taken over at least a one-month period during which time the patients received only placebo medication. The blood pressure was always recorded in both the supine and the upright positions. The patients returned to the clinic at semiweekly intervals during the one-month control period immediately before the experimental drug was started. The postdrug observations on blood pressure are the averages of all observations in the supine and upright positions through the treatment period during which

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TABLE I. SUMMARY OF CLINICAL STATUS AND COMPLICATIONS DUE TO HYPERTENSION PRIOR TO RECEIVING ROXINIL BY MOUTH

	PATIENTS TREATED NO.	AVERAGE AGE	SEX		RACE		RENAL DAMAGE†		CARDIAC FAILURE		ANGINA PECTORIS		ABNORMAL ELECTRO-CARDIOGRAM		CEREBRAL DAMAGE		FUNDI*			
																	1 OR 2+		3 OR 4+	
			MALE NO.	FEMALE NO.	WHITE NO.	NEGRO NO.	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Group 1.—Diastolic Pressure >100 mm. Hg but <120 mm. Hg.																				
Responsive	18	48	8	10	4	14	2	11	4	22	3	17	7	39	2	11	14	78	—	—
Unresponsive	9	52	5	4	2	7	—	—	5	56	1	11	5	56	2	22	8	89	—	—
Total	27	—	13	14	6	21	2	7	9	33	4	15	12	44	4	15	22	81	—	—
Group 2.—Diastolic Pressure more than 120 mm. Hg																				
Responsive	8	46	1	7	4	4	3	38	5	63	2	25	5	63	4	50	6	75	2	25
Unresponsive	5	47	4	1	4	1	4	80	4	80	1	20	3	60	4	80	3	60	2	40
Total	13	—	5	8	8	5	7	54	9	69	3	23	8	62	8	62	9	69	4	31
Grand total	40	—	18	22	14	26	9	23	18	45	7	18	20	50	12	30	31	78	4	10

*Keith-Wagener classification.
†Renal involvement as indicated by a fixed specific gravity and a phenolsulphthalein excretion of less than 10 per cent in 15 minutes.

time the patients returned to the clinic at weekly intervals. All of the patients were carefully studied as to preliminary history and physical examination, complete blood count, urinalysis, blood urea nitrogen, and phenolsulfonphthalein tests, Fishberg concentration tests, chest roentgenograms, and electrocardiograms. These were repeated at two-month intervals during the study. The criterion for inclusion in the study was the presence of an average control blood pressure greater than 150/100 mm. Hg. The criterion for blood pressure responsiveness was a fall of at least 20 mm. Hg in the average mean blood pressure, or a reduction below 150/100 mm. Hg which was considered the normotensive level. In addition to the blood pressure recording, the pulse rate, weight, symptoms and a brief physical examination were made on each clinic visit. Initially, ten patients received 10 mg. of Roxinil per day; fifteen received 20 mg.; and fifteen received 40 mg. It became evident that 10 mg. was inadequate and the dose in the first ten patients was increased to 20 mg. after one month. There was no difference in responsiveness between the 20 and 40 mg. per day doses. The study consisted of twenty-six Negroes and fourteen white patients; eighteen were males and twenty-two were females. The average age was 48 years with a range of 33 to 71 years. The incidence of complications prior to therapy is summarized in Table I.

The severity of the disease is best indicated by the high incidence of complications. Heart failure was present in about one-half of the patients. This was greatest in the patients with diastolic pressure in excess of 120 mm. Hg. It was noted that patients with this complication were particularly resistant to Roxinil therapy as were patients with moderate to severe renal damage.

About one-half of the patients had abnormal electrocardiograms. This was in the form of myocardial ischemia and residuals of previous infarctions in nine patients. The remaining eleven patients with abnormal electrocardiograms showed only left ventricular strain.

About one-third of the patients had evidence of cerebrovascular damage, due either to the hypertension or resulting from presumed associated arteriosclerosis. Four of the patients had previously had cerebrovascular accidents. Four patients had retinal hemorrhages.

RESULTS

The blood pressure response to Roxinil is presented in Table II. The blood pressures taken in upright position are the ones that will be referred to throughout this discussion. Out of the twenty-seven patients with diastolic pressures above 100 mm. Hg but less than 120 mm. Hg (Group I), eighteen (67 per cent) showed a significant blood pressure reduction during period D_1 or D_2, according to the criterion used; i.e., the mean pressure was reduced in excess of 20 mm. Hg. This compares with a response in eight (62 per cent) out of thirteen patients with control diastolic pressures in excess of 120 mm. Hg. Therefore, the rate of responsiveness was not dependent on the severity of the hypertension prior to therapy. However, thirteen (48 per cent) of the patients from Group 1 with less severe abnormality were normotensive (blood pressure less than 150/100

TABLE II. BLOOD PRESSURE RESPONSE TO ROXINIL

PATIENT	SUPINE BLOOD PRESSURE						UPRIGHT BLOOD PRESSURE						PULSE RATE						DIAGNOSIS
	CONTROL		PERIOD D_1		PERIOD D_2		CONTROL		PERIOD D_1		PERIOD D_2		SUPINE			UPRIGHT			
	S	D	S	D	S	D	S	D	S	D	S	D	C	D_1	D_2	C	D_1	D_2	
Control Diastolic Pressure > 100 but < 120 mm. Hg																			
Responsive Patients During Periods D_1 or D_2																			
1. M.E	228	110	189	79	185	88	226	112	203	97	166	93	78	69	78	83	72	81	HCVD, ASHD
2. S.M.	140	108	132	92	139	106	137	109	131	91	143	100	90	76	78	94	83	78	EHVD
3. R.C.	190	108	168	93	160	80	190	110	178	102	166	86	81	74	64	77	73	64	EHVD
4. H.G.	158	109	161	105	138	86	149	109	141	100	128	88	69	69	71	86	83	82	EHVD
5. T.E.	164	114	156	102	138	92	163	119	167	109	137	98	78	60	59	82	74	69	EHVD
6. M.L.	165	98	166	88	200	98	164	103	141	95	170	108	77	62	68	79	62	60	EHVD, AS ID
7. B.H.	190	110	166	92	197	110	178	112	146	92	172	108	77	67	60	83	75	66	HCVD
8. D.L.	171	112	163	103	143	94	177	113	148	99	130	87	98	84	79	113	96	85	EHVD
9. G.A.	165	111	149	96	132	91	175	115	147	102	138	97	85	67	64	89	72	77	EHVD
10. D.I.	155	99	149	85	147	83	175	104	142	79	139	86	86	70	69	98	80	85	
11. W.S.	178	104	166	92	151	91	170	103	155	91	122	79	97	80	79	109	81	93	HCVD, ASHD
12. B.E.	190	95	189	86	186	83	176	100	159	84	140	78	66	60	61	69	65	74	HCVD
13. W.C.	160	105	133	86	136	90	163	113	138	90	137	88	82	73	70	91	81	80	EHVD, ASHD
14. P.H.	170	110	134	90	130	88	150	114	138	98	142	100	92	86	72	93	82	80	EHVD
15. O.C.	155	115	144	88	145	86	155	115	150	88	145	86	80	73	66	82	79	78	EHVD
16. R.W.	150	100	137	94	139	92	154	102	146	94	140	90	76	65	64	110	94	84	EHVD
17. U.H.	152	103	130	86	122	84	150	100	130	86	126	81	86	70	68	88	84	83	EHVD
18. M.F.	167	103	148	88	177	98	188	107	153	90	197	115	76	64	62	89	74	72	HCVD, ASHD
Mean (18 Responsive patients)	169	106	154	91	154	91	169	109	151	94	147	93	82	71	68	90	78	77	
Mean (9 Nonresponsive* patients)	193	107	185	98	188	102	186	107	181	103	181	102	81	67	67	82	69	65	
Control Diastolic Pressure > 120 mm. Hg																			
Responsive Patients During Periods D_1 or D_2																			
19. K.B.	230	139	180	118	176	114	211	140	167	120	169	117	79	70	63	80	78	70	EHVD, ASHD
20. B.W.	188	121	168	104	156	99	197	131	167	116	159	108	80	64	67	83	74	73	EHVD
21. B.P.	225	119	221	108	181	94	227	127	203	112	176	100	92	79	76	104	91	90	HCVD
22. S.E.	199	113	189	95	165	89	221	129	174	96	134	84	87	65	68	82	69	74	HCVD
23. L.M.	206	106	140	90	133	88	196	126	120	80	118	78	92	84	80	94	80	76	HCVD
24. F.O.	237	128	215	111	209	105	207	126	180	100	166	99	74	56	65	80	62	75	HCVD
25. R.T.	210	122	168	98	170	100	207	121	168	103	162	105	81	66	58	80	64	60	HCVD
26. R.E.	268	132	253	115	245	118	261	136	240	118	257	124	87	74	74	93	83	72	HCVD
Mean (8 Responsive patients)	220	123	192	105	179	101	216	130	177	106	168	102	84	70	69	87	75	74	
Mean (5 Unresponsive* patients)	224	136	186	103	206	126	220	132	192	109	210	137	85	71	75	80	72	76	

*Not responsive during either period D_1 or period D_2

S = Systolic blood pressure

D = Diastolic blood pressure

HCVD = Hypertensive cardiovascular disease

ASHD = Arteriosclerotic heart disease

EHVD = Essential hypertensive vascular disease

Period D_1 = Observations after receiving Roxinil for 1 to 3 months

Period D_2 = Observations after receiving Roxinil for 3 to 6 months

mm. Hg) after 3 to 6 months of therapy (Period D_2, whereas only two, or 15 per cent of the patients in Group 2 with more severe disease became normotensive.

When the two periods are compared, four patients (No. 6,7,18,26) were considered unresponsive during period D_2 although they were responsive during the first treatment period (D_1). On the contrary, six patients who were considered unresponsive during period D_1 became responsive during the second treatment period. It may well be that the four patients who were responsive initially and did not continue to obtain an improved pressure effect during period D_2 failed to continue to take the drug consistently. There seemed to be no way to check this completely. The average blood pressure in the Group 1 responsive patients during period D_2 was almost identical with similar observations during period D_1. Likewise, when the average values for the responsive patients in the supine position were compared with those in the upright position, there was very little difference. However, when the mean values during period D_1 for the patients with severe disease are compared with those of D_2, there appears to be a tendency toward a further decrease in pressure.

TABLE III. INCIDENCE OF SYMPTOMS AND SIGNS FOLLOWING THE ADMINISTRATION OF ROXINIL AS COMPARED TO ALSEROXYLON AND RESERPINE

	RESERPINE		ALSEROXYLON		ROXINIL			
					PERIOD D_1		PERIOD D_2	
	NO.	(%)†	NO.	(%)†	NO.	(%)†	NO.	(%)†
Total Number Patients Treated	62	100	118	100	40	100	40	100
Symptom or Sign								
1. Bradycardia*	44	71	77	65	28	70	31	78
2. Sedation	29	47	63	53	20	50	14	35
3. Nasal congestion	40	65	85	72	22	55	21	53
4. Sense of well being	22	35	67	57	16	40	16	40
5. Diarrhea‡	3	5	7	6	5	13	3	8
6. Increased appetite	37	60	72	61	24	60	15	38
7. Weight gain	31	50	73	62	19	48	13	33
8. Fatigue and weakness	27	44	13	11	16	40	13	33
9. Dizziness	13	21	8	7	12	30	5	13
10. Dreams	2	3	7	6	4	10	3	8

†Per cent of total number of patients treated with this drug
*Decrease in pulse rate of 10 beats or more per minute
‡Three movements or more per day
D_1—After treatment for 1 to 3 months
D_2—After treatment for 3 to 6 months

The side reactions to Roxinil, alseroxylon, and reserpine therapy are presented in Table III. There is very little difference between the three compounds. The most annoying complaint following Roxinil therapy was that of nasal congestion, which was experienced by over one-half of the patients. This was usually intermittent and was worse at night. It was severe and distressing in only three instances.

Sedation was a prominent response in the majority of the patients receiving Roxinil. However, this was most prominent during the first two or three weeks of therapy. It decreased with time and by the third month became minimal in most instances.

Weakness and fatigue were observed in about 40 per cent of the cases. This was marked in several instances, and the drug had to be discontinued in two patients because of this. In general, weakness following Roxinil medication was not as severe as during the administration of reserpine. Dizziness, not related to excessive hypotension, was observed in about one-fourth of the patients. Both dizziness and weakness improved and continued therapy. Although polyphagia, weight gain, dreams, and other minor complaints were occasionally observed, these were too mild and too infrequent to be of significance.

A majority of the patients showed an improved sense of well being while receiving Roxinil and headaches were benefited in six out of fourteen patients who presented this symptom as a major complaint prior to therapy. Cardiac failure improved significantly in two instances without change in therapy other than the administration of Roxinil.

DISCUSSION

It would appear that the alkaloidal extract, Roxinil, is at least equally as effective an antihypertensive agent as the other currently available extracts of Rauwolfia serpentina. It reduces the blood pressure significantly in patients with severe hypertensive vascular disease as well as in patients with less severe disease. However, patients in whom the blood pressure is returned to normotensive levels are predominantly from the group with less severe disease.

Initial sedation appears to be less marked with Roxinil as compared to reserpine. This is a definite advantage in some instances where sedation prohibits adequate dosage of reserpine. The initial blood pressure response to Roxinil occurs more rapidly than after the administration of the alseroxylon fraction or after the whole root. In this respect, the onset of action is more like that of reserpine. However, the incidence and severity of side reactions are more nearly akin to those of alseroxylon than they are to those of reserpine.

The blood pressure response to Roxinil as compared to alseroxylon and reserpine is presented in Table IV. Roxinil seemed to be slightly more effective in reducing the blood pressure than were alseroxylon and reserpine. However,

TABLE IV. COMPARISON OF BLOOD PRESSURE RESPONSE TO DIFFERENT EXTRACTS OF RAUWOLFIA SERPENTINA

PREPARATION	PATIENTS TREATED NO.	PATIENTS RESPONSIVE		PATIENTS NORMOTENSIVE	
		NO.	(%)	NO.	(%)
Alseroxylon	118	60	51	39	33
Reserpine	62	29	47	14	23
Roxinil	40	26	65	13	33

the difference in effectiveness was not great and in fact may be more apparent than real due to the relatively small number of patients who received Roxinil. At best there appears to be little difference in blood pressure response to the three different extracts evaluated by the authors under similar conditions of study.

SUMMARY AND CONCLUSIONS

1. Forty patients with essential hypertension of variable severity have been treated with Roxinil, an extract of Rauwolfia serpentina containing multiple alkaloids. These results were then compared with those obtained with the alseroxylon fraction as well as the pure alkaloid, reserpine.

2. Roxinil is an effective agent for reducing the blood pressure in patients with hypertension. It reduces the pressure in patients with severe disease as well as in patients with disease of mild to moderate severity. However, the patients in whom the pressure returned to normotensive levels were predominantly from the group with less severe disease.

3. The blood pressure response, side reactions, and general clinical responses with Roxinil were quite similar to those observed with other extracts of Rauwolfia serpentina.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Quaranta patientes con hypertension essential de variabile severitate esseva tractate con Roxinil, un extracto de *Rauwolfia serpentina* continente multiple alkaloides. Le resultatos esseva comparate con le resultatos obtentite (1) con le fraction alseroxylona e (2) con le alkaloide pur, reserpina.

2. Roxinil es un agente efficace in reducer le pression sanguinee in patientes con hypertension. Illo reduce le pression in casos de leve o moderate severitate e etiam in patientes con formas sever del morbo. Il es a notar, nonobstante, que le patientes in qui le pression recedeva a nivellos normotensive pertineva principalmente al gruppo de casos minus sever del morbo.

3. Le responsa del pression sanguinee, le reactiones accessori, e le effectos clinic general post le uso de Roxinil esseva simile a illos observate post le uso de altere extractos de *Rauwolfia serpentina*.

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CAUTION AGAINST THE USE OF MEPERIDINE HYDROCHLORIDE (ISONIPECAINE, DEMEROL) IN PATIENTS WITH HEART DISEASE, PARTICULARLY AURICULAR FLUTTER

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THE possible harmful effects of meperidine hydrochloride in one case of auricular flutter prompted the revaluation of this drug in patients with heart disease, particularly those having auricular flutter.

Review of the literature reveals that meperidine has certain features in common with a variety of drugs including atropine, quinidine, procaine, papaverine, and benadryl, both chemically[1,4,12] and pharmacologically.[1-11] Certain effects such as analgesia, sedation, and spasmolysis make meperidine a drug of great clinical value. Other effects such as depression of myocardium[1,7] and lowering of the blood pressure[13] are usually not marked nor clinically obtrusive. It has been clearly shown that meperidine, atropine, and quinidine resemble each other pharmacologically,[4,7-9] especially in their ability to antagonize the action of acetylcholine. The anticholinergic atropine-like action of meperidine in insulating the heart against vagal stimuli has been well demonstrated[2,6,11] and is probably due to a direct action on postganglionic vagal nerve endings. Reflex loss of vagal tone may also occur secondary to lowering of blood pressure after meperidine. It is well known clinically that atropine may decrease carotid sinus reflex sensitivity and, by releasing vagal inhibition of the A-V node, inhibit the vagal action of digitalis. This is sometimes evidenced by the occurrence of A-V dissociation, shortening of P-R interval, or decrease in heart block. Similarly, it is frequently observed that quinidine may inhibit the sensitivity of the carotid sinus reflex and prevent or decrease the vagal effect of digitalis. Because of the pharmacological similarity of meperidine to quinidine and especially to atropine, one would anticipate similar effects in patients receiving meperidine. In regard to its atropine-like action, 100 to 150 mg. of meperidine given intravenously to twenty-six normal subjects caused an increase in pulse rate of an average of 11 beats per minute;[14] in six subjects the rate rose over 22 beats per minute, and in two individuals over 30 beats per minute. It is also interesting that patients addicted to meperidine or atropine often display many symptoms in common, including tachycardia.[5,15]

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In the case of auricular flutter, atropine may quickly change the ventricular rate from, say 85 in a 4:1 response to 170 with a 2:1 block. If the atropine-like action of meperidine is significant, one would anticipate theoretically a similar effect in auricular flutter. No data could be found in the literature regarding the effect of meperidine in patients with such cardiac arrhythmias.

We believe that the following cases demonstrate an important action of meperidine which, if unrecognized, may prove harmful or even fatal in some cases.

CASE REPORTS

CASE 1.—A 27-year-old white male was referred for evaluation regarding surgical treatment of rheumatic heart disease with severe aortic insufficiency.

Electrocardiograms on admission showed auricular fibrillation with an average rate of 140 and aberrant ventricular response. The arrhythmia was easily reverted to normal sinus rhythm on the third day following administration of additional digitalis and relatively small doses of quinidine.

After careful medical preparation, a plastic aortic valve prosthesis was inserted in the first portion of the descending aorta without complications. Postoperative medication included 0.15 mg. digitoxin daily, 0.3 Gm. quinidine four times a day, and meperidine 50 mg., intramuscularly every four hours. The postoperative course was uneventful until the fourth day when tachycardia developed. The electrocardiograms revealed auricular flutter, auricular rate 312 with varying A-V response, ventricular aberrancy, and a ventricular rate of about 150. Oral digitoxin and intravenous Cedilanid were then given in an attempt to slow the ventricular rate. Oral quinidine in increasing individual doses up to 0.9 Gm. was unsuccessful. Because of apprehension, and pain at the operative area, the four hourly meperidine had been increased to 75 mg. In spite of the digitalis and quinidine therapy, the arrhythmia persisted with frequent sudden increases in ventricular rate, often up to 170, for no apparent reason (Fig. 1). Prostigmin, 0.5 to 0.75 mg. intramuscularly, proved to be most beneficial in producing temporary lowering of ventricular rate by increasing the degree of A-V block. However, the patient's condition began to deteriorate with signs of increasing cardiac decompensation. All possible factors that could contribute to the refractoriness of the arrhythmia were revaluated, and the relationship of meperidine administration to the sudden increases in ventricular rate was then suspected. From the nurse's notes comparison of the pulse charted with the time of meperidine injection revealed a close correlation between recorded episodes of rapid pulse rate and the preceding injection of meperidine. As indicated in Fig. 1, eight recorded episodes of tachycardia followed a meperidine injection by 30, 30, 0 (?), 10, 30, 30, 180 (?), and 30 minutes. The exact time of onset of the episodes of tachycardia could not be determined from the available information. For example, the episodes recorded at 0 and 180 minutes after meperidine may have had their onset shortly after the injection in each case. Review of the numerous electrocardiograms revealed that by coincidence several were taken a known time shortly before and after meperidine injection. These showed the development of a low grade A-V block with fast ventricular rate following meperidine administration. In Fig. 1 the electrocardiogram strips represent a typical example of the changes that occurred.

After 8 days of this uncontrollable arrhythmia, methadone hydrochloride was substituted for meperidine, and the rapid heart action ceases to be a problem. Digitalis was effective in slowing the rate, and five days later reversion to normal sinus rhythm was accomplished. The subsequent postoperative course was smooth, and he was discharged improved on the forty-first day.

Comment: Meperidine appeared to be responsible for the frequent sudden marked increases in ventricular rate. Because of serious underlying heart disease this resulted in increasing cardiac decompensation which showed no improvement until slowing of the heart rate occurred following withdrawal of

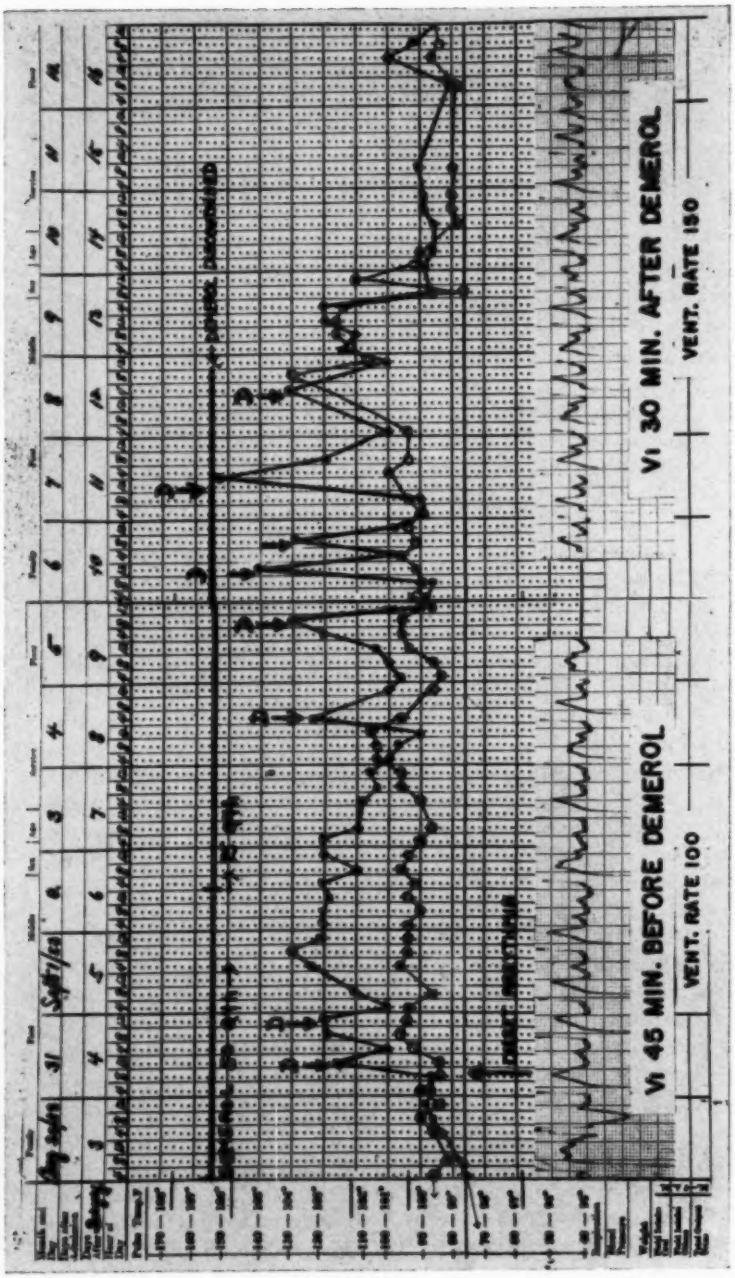

Fig. 1.—Male, aged 27 years, rheumatic aortic insufficiency. Postoperative from aortic valve surgery. Note apparent relationship between episodes of tachycardia and prior injection of meperidine. Representative strips of V_1 are shown, taken before and after one such injection of meperidine that was followed by tachycardia. Note increase in rate from 100 to 150 due to decrease in A-V block.

meperidine. It is felt that the control of the tachycardia may have been life-saving in this particular case.

CASE 2.—A 73-year-old white male was admitted with auricular flutter. There was a history of repeated episodes of auricular arrhythmias over the previous thirty years with no evidence of underlying heart disease.

Examination revealed a well preserved eldery white male in apparent good health. Blood pressure was 120/80 mm. Hg. A Grade 2 apical systolic murmur was noted. Detailed clinical and laboratory examinations were not revealing apart from the cardiac arrhythmia. The electrocardiogram revealed auricular flutter, with varying A-V block mostly 2:1 or 1:1 (Fig. 2,*A*).

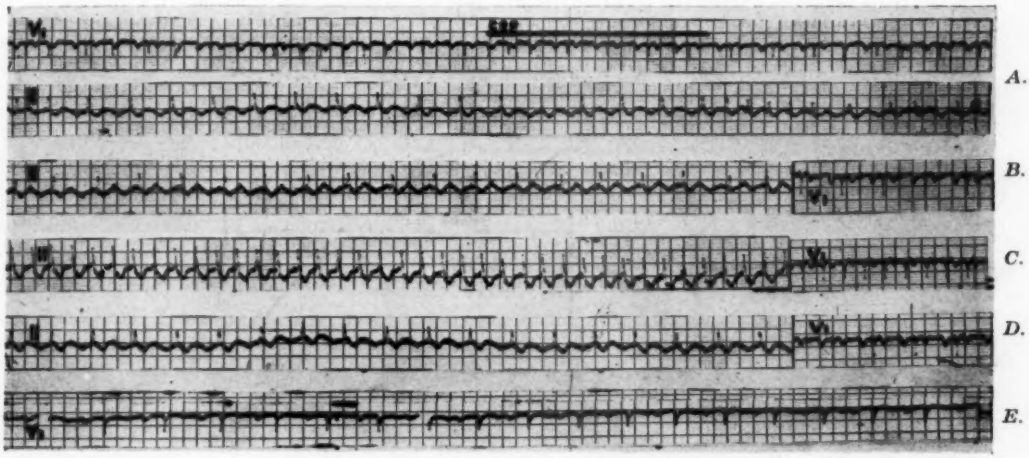

Fig. 2.—73-year-old male. "Normal fibrillator," paroxysmal for 30 years. *A*, Auricular flutter with varying A-V block, mostly 2:1 or 1:1. Auricular rate 188, average ventricular rate 122. *B*, Following 0.8 mg. of Cedilanid intravenously. Note constant 2:1 response, ventricular rate 94. *C*, 20 minutes after 100 mg. of meperidine intramuscularly. Note constant 1:1 response with doubling of ventricular rate to 188. *D*, 40 minutes after *C* and 20 minutes after 0.75 mg. Prostigmin intramuscularly. Ventricular rate returned to previous 94 with constant 2:1 response. *E*, Three hours later after an additional 0.4 mg. of Cedilanid intravenously. Normal sinus rhythm.

The auricular rate was 188, and the ventricular rate 122. Cedilanid, 0.8 mg. given intravenously, changed the block to a constant 2:1 with ventricular rate of 94 (Fig. 2,*B*). Thirty minutes later 100 mg. of meperidine was given intramuscularly, and this was followed in twenty minutes by a doubling of the ventricular rate to 188 with a constant 1:1 response (Fig. 2,*C*). This rapid rate continued for twenty minutes, at which point 0.75 mg. of Prostigmin was given intramuscularly. Twenty minutes later the ventricular rate dropped back to 94 again with a constant 2:1 block (Fig. 2,*D*). He was then given an additional 0.4 mg. of Cedilanid intravenously (total 1.2 mg.) and about three hours later the electrocardiogram revealed a normal sinus rhythm, rate 68.

Comment: Meperidine appeared to be directly responsible for a sudden dramatic doubling of the ventricular rate from a benign 94 to a serious level of 188, which if untreated in this elderly gentleman would have led to serious difficulty.

CASE 3.—A 42-year-old white male was admitted because of rapid irregular heart action, nausea, and vomiting. At the age of 16 he first noticed episodes of severe palpitation which recurred once or twice a month until the age of 35. After this they became progressively more frequent. During the three weeks prior to admission they occurred as often as five to ten times daily. Nausea, vomiting, and headaches often were associated.

About twelve years previously, he was first told he had hypertension and again one year before admission was referred to the outpatient department for evaluation of hypertension. Blood pressure on four or five occasions ranged between 130/100 to 170/130 mm. Hg. Benzodioxane and cold pressor tests were negative. After a short trial of medical therapy he stopped reporting to the clinic.

Two days prior to admission, because of symptoms suggestive of peptic ulcer, he was placed on antacid and tincture of belladonna, 10 drops three times a day. This medication greatly relieved his epigastric distress but his paroxysms of palpation seemed to be more severe. The episodes of palpation progressively increased until they were practically continuous.

Physical examination revealed a man sweating profusely, retching, and complaining of nausea and palpitation.

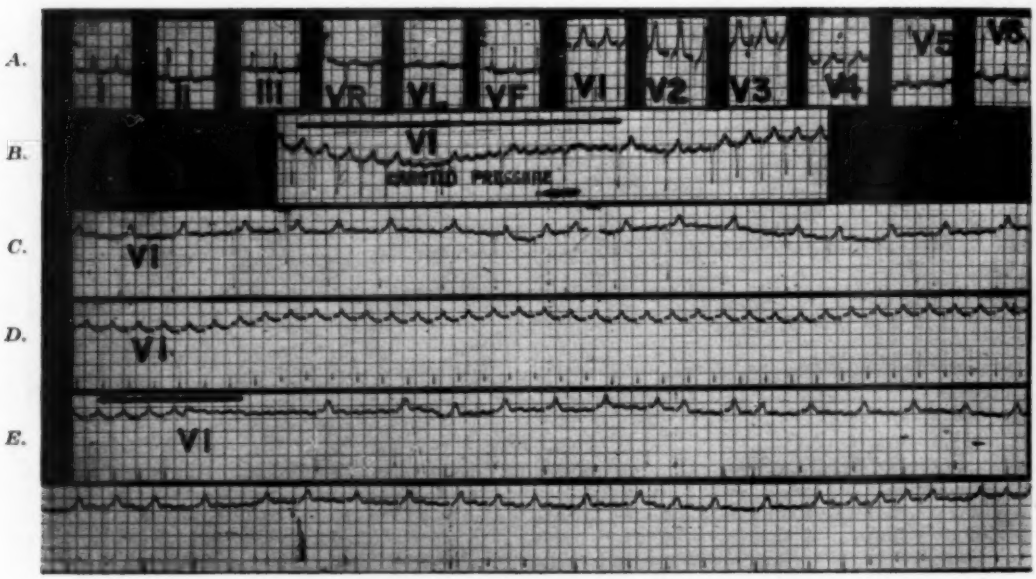

Fig. 3.—Male, aged 42 years with pheochromocytoma and paroxysmal auricular flutter. *A*, 2:1 block. Ventricular rate 166. *B*, Carotid sinus pressure temporarily causes slowing of ventricles demonstrating typical flutter waves. *C*, After 4.0 mg. of Cedilanid intravenously. Note varying A-V block. Ventricular rate 72. *D*, 20 minutes after 100 mg. meperidine intramuscularly. Rate has doubled to 150. *E*, Temporary slowing with carotid sinus pressure. Flutter waves again demonstrated.

Blood pressure 130/105 mm. Hg; pulse 166 and regular; Grade 2 hypertensive retinopathy was present. Heart was unremarkable except for a Grade 2 systolic apical murmur and a third heart sound in diastole felt to be either a ventricular diastolic gallop or auricular sound. The rest of the examination was not revealing.

The electrocardiogram on admission showed auricular flutter with 2:1 response and a ventricular rate of 166 (Fig. 3,*A*). Carotid sinus pressure increased the A-V block and slowed the rate with the typical "jerky" return characteristic of flutter (Fig. 3,*B*). In an effort to control the fast ventricular rate, a total of 4.0 mg. of Cedilanid divided in ten doses was given over the next 24 hours. At the end of this time auricular flutter was still present with varying A-V block and a ventricular rate of 72 per minute (Fig. 3,*C*).

At this time meperidine 100 mg. was given intramuscularly, and the heart rate checked at frequent intervals. After 20 minutes the rate essentially doubled to 150 with a 2:1 block (Fig. 3,*D*). Carotid sinus pressure (Fig. 3,*E*) temporarily slowed the ventricular rate. However, the fast rate persisted over the next 70 minutes and then began to slow until two hours later the rate was 80 to 85.

The following morning another control tracing (Fig. 4,*A*) showed a rate of 85 with persistence of auricular flutter and varying block mostly 4:1. Carotid sinus pressure resulted in temporary slowing of the ventricular rate with a jerky return (Fig. 4,*C*).

Again 100 mg. of meperidine was given and within 30 minutes the ventricular rate began to increase. The predominantly 4:1 block gradually shifted to 2:1 block until at the end of an hour the ventricular response was a constant 2:1 with a rate of 140. (Fig. 4,*D*). After 20 minutes at this rate 1.0 mg. of Prostigmin was given intramuscularly. This was followed in 15 minutes by slowing of the ventricles due to an increase in A-V block.

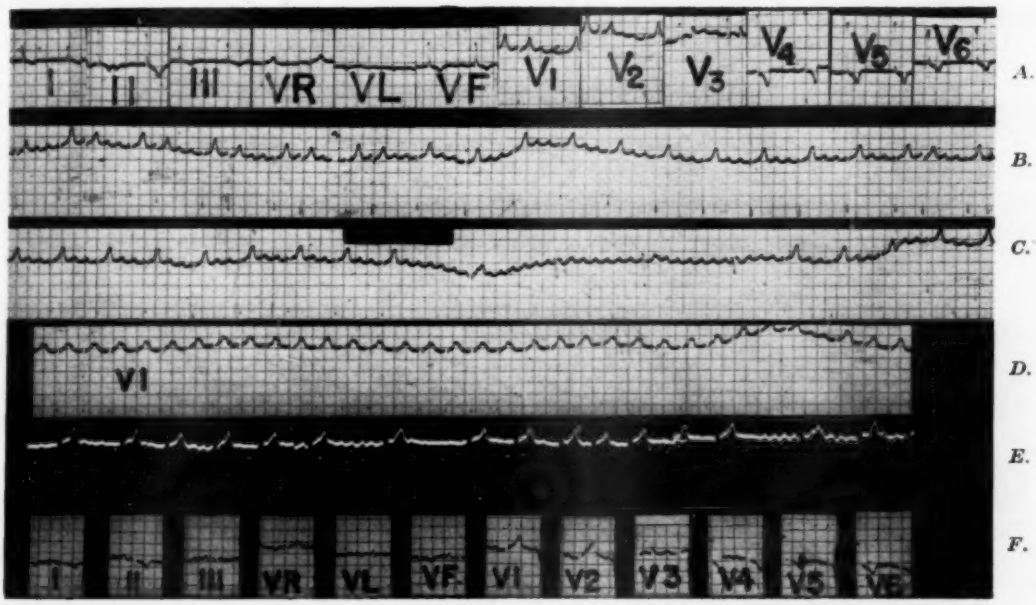

Fig. 4.—Same patient as Fig. 3. *A* and *B*, Flutter with varying block. Average ventricular rate 85. *C*, Carotid sinus pressure. *D*, 60 minutes after 100 mg. meperidine intramuscularly. Note increase in ventricular rate to 140. Constant 2:1 block. *E*, 40 minutes after Prostigmin. Rate decreased to 72. *F*, 2 days later. Normal sinus rhythm.

The electrocardiogram taken 40 minutes after Prostigmin injection showed the appearance of a flutter-fibrillation. The ventricular rate had decreased back to its original 70 to 75 (Fig. 4,*E*). Quinidine and digitalis were stopped. After two days he reverted to normal sinus rhythm (Fig. 4,*F*).

Two days later he had a recurrence of auricular flutter (auricular rate 272 with a constant 2:1 A-V block; ventricular rate 136). After 2.8 mg. of intravenous Cedilanid, given in divided doses, he responded readily to carotid sinus pressure with an increase in A-V block and resultant slowing of the apical rate. After a total of 4.0 mg. of Cedilanid the ventricular rate decreased to 84 with varying 2:1 and 4:1 block. At this point meperidine, 100 mg. intramuscularly, was given and was followed 10 minutes later by a speeding up of the ventricular rate to 100 with more frequent 2:1 response.

Thirty minutes after meperidine the ventricular rate was 108 with a predominantly 2:1 response. The auricular rate had remained unchanged.

The following morning flutter was still present with a varying 2:1 and 4:1 response and a ventricular rate of 92. Meperidine, 80 mg. intramuscularly, was given and 5 minutes later the ventricular rate had increased to 128 with a predominantly 2:1 response. Twenty minutes after meperidine the ventricular rate was 120 and remained at this level for about 2 hours. At this point Prostigmin, 0.75 mg. intramuscularly, was given, and in 25 minutes the ventricular rate was found to have dropped to 68 with a constant 4:1 A-V block.

Following reversion to normal sinus rhythm with quinidine, he was discharged. A Regitine test was negative.

Although on maintenance digitalis and quindine, his heart began to flutter one week later, and he was readmitted. His ventricular rate was slowed with intravenous Cedilanid and on the sixth hospital day auricular flutter with a varying A-V block (2:1, 4:1 alternating) was present (Fig. 5,*A*). The auricular rate was 280 and the ventricular rate, 96.

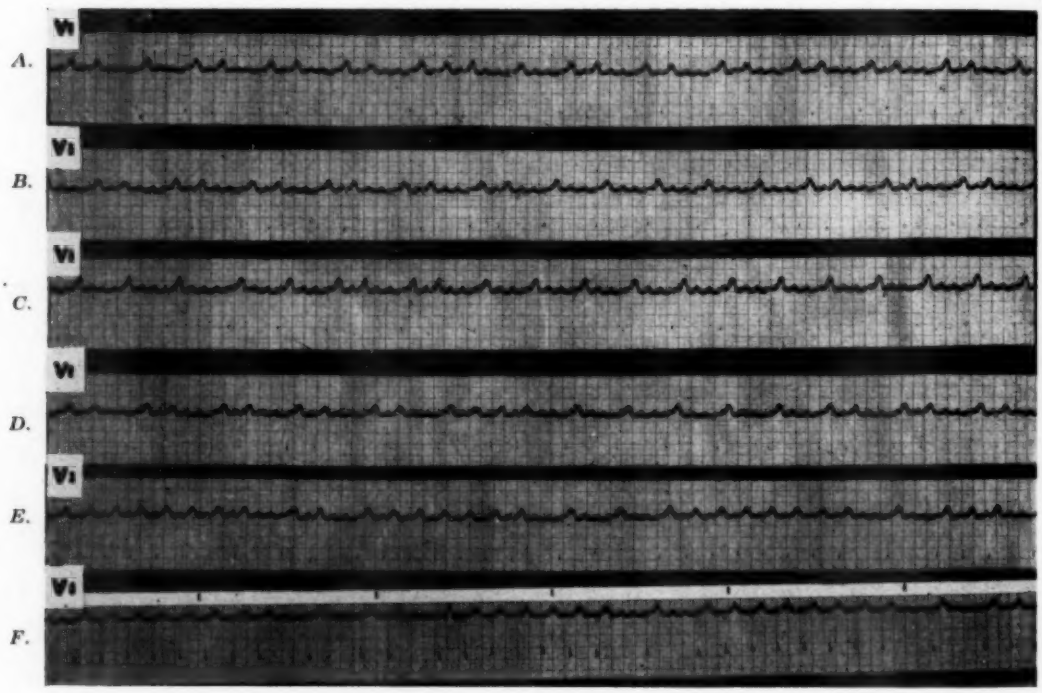

Fig. 5.—Same patient as Fig. 3. Another episode of flutter. *A*, Varying block (2:1, 4:1). Ventricular rate 96. *B*, 45 minutes after 5 mg. methadone intramuscularly. Rate 84. *C*, 120 minutes after methadone. Rate 77. *D*, 5 hours after methadone. Rate 92. *E*, 45 minutes after meperidine. Rate has increased to 110. *F*, Persistence of rate as in *E* 70 minutes later.

Methadone, 5 mg. intramuscularly, was then given and at no time did the ventricular rate increase. At the end of 45 minutes the apical rate was 84 (Fig. 5,*B*). One-hundred and twenty minutes after methadone the ventricular rate was 77. The auricular rate had not changed, and there was slight slowing of the ventricular rate (Fig. 5,*C*).

Five hours after methadone the rate had again returned to 92 (alternating 2:1 and 4:1 block; Fig. 5,*D*). At this time meperidine, 100 mg. intramuscularly, was given and within 45 minutes the rate had increased to 110 with runs of 2:1 response interrupted every 7 or 8 beats with a 4:1 A-V response (Fig. 5,*E*). This was still present 70 minutes after the injection (Fig. 5,*F*).

Because of elevation of blood pressure during one of his typical attacks of palpation, histamine and Regitine tests were done. The results were unusual but the concensus of opinion was that the presence of a pheochromocytoma was likely. Such a tumor was found at operation involving the left adrenal gland. This was successfully removed.

On only one occasion postoperatively did the patient develop an arrhythmia. This consisted of auricular flutter with an auricular rate of 270 and varying ventricular response. Meperidine, 100 mg. intramuscularly, was again administered. Six minutes prior to injection the ventricular rate was 78 and immediately prior to injection, 68. Following meperidine there was an increase in heart rate due to decrease in A-V block and average ventricular rates recorded at

7, 17, and 22 minutes were 86, 90, and 94, respectively. Fifty-two minutes after injection the ventricular rate was 85. The arrhythmia subsequently easily reverted to normal sinus rhythm, and the patient has had no further attacks.

Comment: Meperidine repeatedly caused an increase in the ventricular rate of this patient having recurrent episodes of auricular flutter. The accelerated heart rate was believed to be related to the atropine-like action of meperidine releasing vagal tone and decreasing A-V block (e.g., 4:1 to 2:1, etc.)

One can only speculate as to the possible effects of the pheochromocytoma regarding the response of the auricular flutter to meperidine in this case. It is certainly possible that the action of meperidine may have been enhanced by the presence of the tumor.

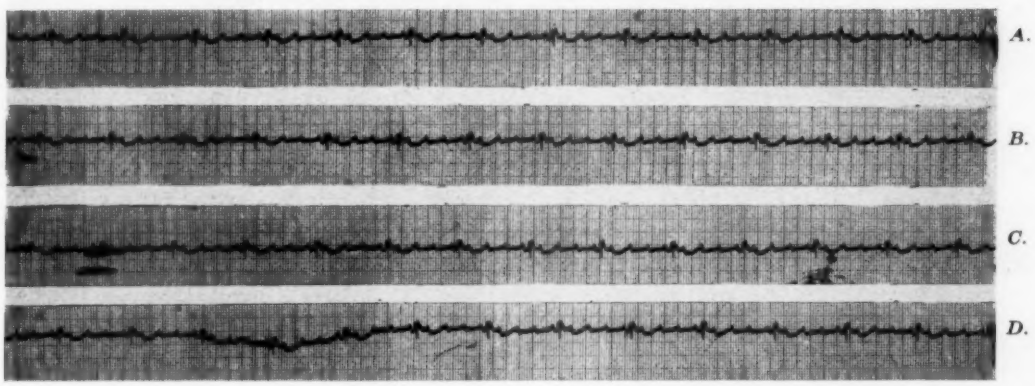

Fig. 6.—81-year-old male with hypertensive arteriosclerotic heart disease, auricular flutter and congestive failure. *A* and *C*, Strips of Lead V_1, each taken before an injection of 100 mg. of meperidine. *B* and *D*, Representative strips of Lead V_1, taken after injection of meperidine. No change in rate.

CASE 4.—An 81-year-old white male was admitted for therapy of moderate congestive failure on the basis of hypertensive arteriosclerotic heart disease. The initial electrocardiogram revealed auricular flutter with an auricular rate of 280 and varying A-V response. The ventricular rate was in the range of 100 (Fig. 6). After digitalization his rhythm became a 4:1 flutter (auricular rate 226, ventricular rate 56). No change in ventricular rate occurred following the administration of 100 mg. of meperidine on two occasions (Fig. 6).

CASE 5.—A 46-year-old woman entered the hospital for surgical treatment of mitral stenosis.

On physical examination she was found to have the classical signs of mitral stenosis with an accentuated mitral first sound, a Grade 4 diastolic rumble, and a prominent opening snap.

The electrocardiogram on admission revealed auricular flutter with an auricular rate of 300 and changing A-V block with an average ventricular rate of 100. She had not been taking digitalis. On the fifth hospital day after a control electrocardiogram she received 100 mg. of meperidine intramuscularly. Electrocardiograms taken at frequent intervals thereafter failed to reveal any significant change in heart rate. She was then digitalized with 1.2 mg. digitoxin, in divided doses, and meperidine was administered again. There was no significant change in the heart rate following meperidine.

Comment: Injection of meperidine failed to produce any change in heart rate in the above two patients, with auricular flutter. An unknown proportion of patients with auricular flutter will undoubtedly fit into this group and show no increase in ventricular rate with meperidine administration.

CASE 6.—A 53-year-old white male was admitted with moderate congestive heart failure due to hypertensive and arteriosclerotic heart disease.

The initial electrocardiogram revealed auricular flutter and myocardial changes.

During the first six hospital days the patient received a total of 2.4 mg. of Cedilanid intravenously and 1.1 Gm. of digitalis leaf orally in addition to mercurials and Diamox.

On the sixth hospital day, a repeat electrocardiogram showed auricular flutter with classical flutter waves in Leads II, III, and VF and clear-cut P waves in V_1, auricular rate 334 (Fig. 7,*A*).

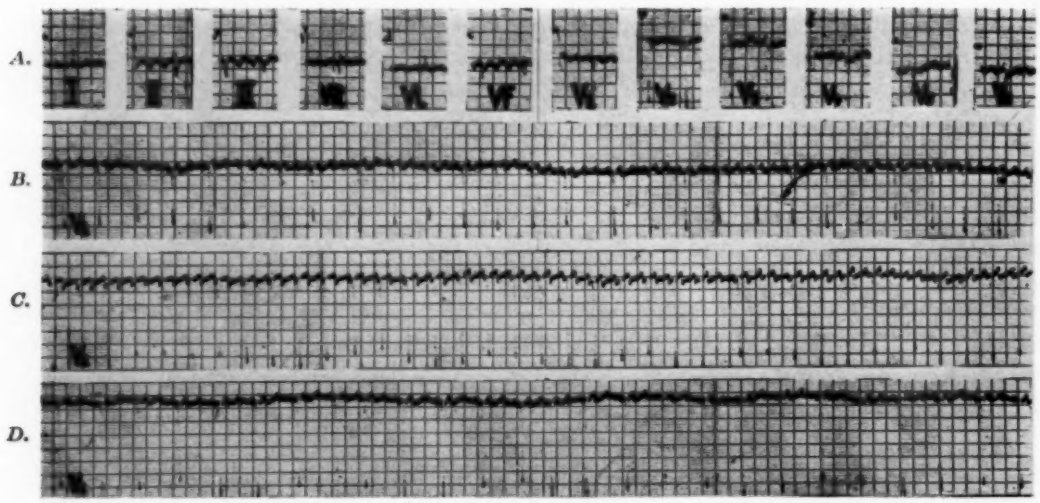

Fig. 7.—53-year-old white male with hypertensive arteriosclerotic heart disease. *A* and *B*, auricular flutter, auricular rate 334, varying ventricular response, ventricular rate 112. *C*, Twenty-five minutes after 100 mg. of meperidine intramuscularly. Ventricular rate, 144. *D*, Forty minutes after meperidine. Ventricular rate 104.

A control one-minute strip of V_1 taken two minutes prior to intramuscular injection of 100 mg. of meperidine revealed auricular flutter with varying A-V block and a ventricular rate of 112 (Fig. 7,*B*). Following meperidine injection, eight one- or two-minute strips of V_1 were taken over the next forty minutes. These revealed a gradual decrease in A-V block with speeding up of the ventricular rate until at 25 minutes following meperidine, there was an almost constant 2:1 response with a ventricular rate of 144 (Fig. 7,*C*). Over the next 15 minutes there was a gradual slowing of ventricular rate with an increase in A-V block and varying ventricular response; 40 minutes after injection the ventricular rate was 104 (Fig. 7,*D*). There was no increase in symptomatology during the tachycardia.

Comment: One injection of meperidine in this 53-year-old male, having moderate congestive failure, increased the ventricular rate from 112 to 144. The tachycardia was well tolerated because of its relatively short duration.

It is felt that repeated injections would have led to worsening of the cardiac decompensation and interfered with therapy of the congestive failure.

CASE 7.—A 44-year-old Negro female entered the hospital for evaluation of hoarseness due to left vocal cord paralysis. A diagnostic workup revealed that she had mitral stenosis, and she subsequently underwent cardiac surgery at which time the presence of a tight mitral stenosis was confirmed and a mitral valvulotomy performed.

On the tenth hospital day, a control electrocardiogram prior to meperidine injection revealed right ventricular hypertrophy and auricular flutter, auricular rate 312, varying ventricular response, and ventricular rate of 88 (Fig. 8,*A* and *B*). Numerous one- or two-minute strips of

V_1, taken at 4 or 5 minute intervals after injection of 100 mg. of meperidine showed a gradual decrease in A-V block with an increase in the ventricular rate; nineteen minutes after meperidine injection the ventricular rate had increased to 120 (Fig. 8,*C*) and at 26 minutes the rate reached a maximum of 148 (Fig. 8,*D*). A gradual decline in rate then occurred until at 36 minutes it was recorded at 124 (Fig. 8,*E*). No untoward symptoms occurred during this episode of tachycardia.

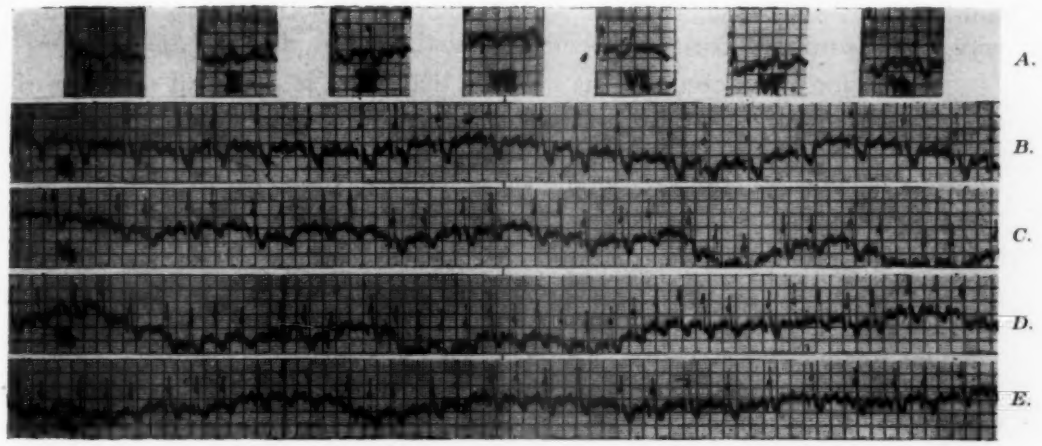

Fig. 8.—44-year-old Negro female postoperative from mitral commissurotomy. *A* and *B*, Control electrocardiogram prior to injection of meperidine. Auricular flutter, ventricular rate 88. Right ventricular hypertrophy. *C*, Nineteen minutes after injection of 100 mg. meperidine intramuscularly. Ventricular rate 120. *D*, Twenty-six minutes after meperidine. Ventricular rate, 148. *E*, Thirty-six minutes after meperidine. Ventricular rate, 126.

Two days later a control electrocardiogram prior to meperidine injection revealed auricular flutter with an auricular rate of 334, varying A-V response, and a ventricular rate of 99. Following the injection of 100 mg. meperidine there was a general decrease in A-V block with increase in ventricular rate to 100 at 6 minutes, and 132 at 26 minutes. The ventricular rate then gradually declined to 96 at 31 minutes after injection of meperidine. No untoward symptoms occurred during this episode of tachycardia.

Comment: Meperidine injection produced an increase in heart rate of 60 and 44 beats per minute in this patient with auricular flutter postoperative from mitral commissurotomy. The tachycardia was well tolerated. It is suspected that if the fast rates had been produced prior to opening of the mitral valve, symptoms might have resulted.

DISCUSSION

The deleterious effect of an increase in heart rate, especially in patients with myocardial, valvular, or coronary artery disease, has been repeatedly stated and is commonly observed clinically. For example, a patient with no organic heart disease who develops an arrhythmia with a fast ventricular rate such as 170 may over a period of 24 to 48 hours gradually develop cardiac dilatation, congestive failure, and occasionally electrocardiographic evidence of myocardial ischemia. It is not until the heart rate is slowed that the abnormal findings disappear. Similarly, patients with heart disease may maintain cardiac compensation at rates of 80 or 90, but with an increase in rate to 110 or 120 from such causes as apprehension, fever, etc., they may develop signs of congestive failure.

The beneficial effect of a slow heart rate is further suggested by the relative infrequency of the classical findings of congestive failure in patients with complete heart block having very slow ventricular rates. The relatively frequent presence of slow heart rates, such as complete heart block, in patients with silent infarcts[16] and the relief of anginal pain by slowing of the heart rate with carotid sinus pressure[17] also suggest the beneficial effect of a slow heart rate with reference to myocardial nutrition.

All the foregoing observations indicate that there is a critical duration of diastole necessary for biochemical recovery of the myocardium. In patients with heart disease the diastolic recovery period is frequently prolonged. With tachycardia, diastole is shortened and the diastolic recovery period is encroached upon resulting in a detrimental effect on myocardial function. For this reason a slight increase in ventricular rate of only 15 to 20 beats per minute may precipitate anginal pain or congestive failure.

A slight increase in heart rate may also prove harmful in patients with valvular disease and a relatively healthy myocardium. For example, patients with mitral stenosis frequently show a close correlation between the development of episodes of pulmonary edema and the rate of mitral valvular blood flow,[18] the latter depending on numerous factors, one of the most important being heart rate.

Auricular flutter represents an almost unique situation in which the ventricular rate is dependent upon a critical degree of A-V block which is often readily modified by slight changes in vagal tone. Marked changes in ventricular rate due to changes in A-V block may occur because of numerous factors which influence vagal reflexes. Cases of auricular flutter with 2:1 A-V block and a ventricular rate of say 150 are commonly seen where digitalis, Prostigmine, carotid sinus pressure, or elevation of blood pressure by pressor agents may suddenly change the degree of A-V block to 3:1 or 4:1 with a drop in ventricular rate to 100 or 75. On the other hand, atropine may decrease A-V block in auricular flutter as noted previously.

In view of the results obtained with the patients described previously, it is felt that meperidine has a definite atropine-like action in decreasing A-V block with resultant increase in ventricular rate. Because of the large number of variables in patients receiving meperidine such as dose and route of administration, degree of vagal tone and sensitivity to the drug, concomitant use of other drugs, intrinsic disease of the conduction tissue or myocardium, etc., one cannot anticipate a significant increase in heart rate in all patients with auricular flutter. However, we believe that a high percentage of patients will demonstrate this response which will assume serious significance in some cases.

SUMMARY

Our interest in the possible harmful effects of meperidine in patients with heart disease was stimulated by the observation of meperidine-induced tachycardia in one patient with auricular flutter.

Certain aspects of the pharmacology of meperidine and the deleterious effects of rapid heart action in patients with heart disease are reviewed. Theo-

retical considerations would appear to indicate that meperidine, by means of its anticholinergic action, is capable of producing tachycardia particularly in auricular flutter.

Cases are presented which demonstrate this action and its possible harmful effects in certain clinical situations.

It is suggested that meperidine be used with caution in selected cases of heart disease, particularly those having auricular flutter.

SUMMARIO IN INTERLINGUA

Nostre interesse in le possibilitate que le effectos de meperidina es nocive in patientes cardiac esseva inspirate per le observation de un tachycardia causate per meperidina in un patiente con flutter auricular.

Nos discute certe aspectos del pharmacologia de meperidina e le effectos nocive de rapide activitate del corde in patientes cardiac. Super le base de considerationes theoric il nos pare permittite concluder que le potentia anticholinergic de meperidina qualifica iste droga a producer tachycardia specialmente in casos de flutter auricular.

Nos presenta un serie de casos que demonstra iste action e su possibile effectos nocive in certe situationes clinic.

Nos opina que in certe casos cardiac, specialmente in casos con flutter auricular, meperidina debe esser usate con grande circumspection.

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THE USE OF PROCAINE AMIDE (PRONESTYL) TO ACCELERATE BLOOD TRANSFUSIONS IN THE ANESTHETIZED PATIENT: ITS GENERALIZED SYMPATHOLYTIC EFFECT WITHOUT HYPOTENSION

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IN THEIR report Neustrup and Milowsky[1] have advocated the use of procaine to accelerate the administration of blood transfusions in the anesthetized patient. They proposed the use of 0.5 to 1.0 Gm. of procaine mixed with blood in a 500 c.c. container to affect the local venospasm associated with the transfusion of refrigerated blood. With such a procedure they were able to obtain rates of blood flow of over one hundred drops per minute, and the administration of 500 c.c. of blood was completed consistently within 10 to 30 minutes.

We have used procaine in the same fashion with similar results. In chest surgery, not only is substantial blood loss a frequent problem, but the use of procaine in blood serves a second purpose as a prophylactic against cardiac arrhythmias.[2,3] However, with the advent of Pronestyl and its general acceptance as a more specific agent in the prevention and control of cardiac arrhythmias,[4-7] procaine was displaced in favor of the newer substance. In addition to being a more specific agent in cardiac arrhythmias, Pronestyl is a much safer drug than its parent substance especially as regards its toxic manifestations on the central nervous system. It has been used by us prophylactically in chest operations and in cardiac arrhythmias which developed in the anesthetized patient during any surgical procedure. The method followed was to inject 100 to 200 mg. intravenously in a period of two to three minutes. This is the rate recommended by Kayden and associates.[6] In chest surgery, as much as 1.0 to 2.0 Gm. of Pronestyl has been slowly injected in divided doses using this time basis. Approximately 0.5 to 1.0 Gm. was given in the period prior to opening the chest. It soon became evident that the injection of Pronestyl was attended frequently with severe and alarming drops in blood pressure. This side reaction has been noted by others.[5,6] Stearns and associates[8] noted significant hypotension after total doses ranging from 70 to 800 mg., even when the rate of injection was reduced to 25 to 100 mg./min. The fall in blood pressure was apparently not related to total dosage, but more to the rate of injection. They emphasized that the hypotensive effect of Pronestyl constitutes a serious hazard and that the recommended rate of 100 to 200 mg./min. for intravenous administration appears to be excessive. We found that we could usually avoid this reaction by injecting Pronestyl in 1.5 to 2 times the recommended time. However, this resulted in a significant loss of time for the anesthesiologist. It became evident that the mixture of Pronestyl with blood would solve this problem

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The statement and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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and at the same time it was expected that the Pronestyl would act similarly to procaine in accelerating the rate of blood transfusions. Accordingly, 0.5 to 1.0 Gm. Pronestyl was mixed with each 500 c.c. of blood. No untoward effects were noted in the appearance of the blood.

RESULTS

There was no drop in systolic or diastolic blood pressure that could be correlated with the use of approximately 400 units of blood-Pronestyl mixture by this method in all types of surgery. Pronestyl was used mainly in abdominal and chest cases. In the former, Pronestyl was used only when blood flow rate was slow and inadequate for the needs of the patient. In chest cases Pronestyl was usually given prophylactically with blood. Ether and cyclopropane or a combination of the two were the most common anesthetic agents.

The effect on the rate of blood flow was at least equal to that of procaine. Rates of flow of 300 to 400 drops per minute (after the rate had slowed to 20 to 40 drops per minute) were consistently obtained, and occasionally the blood flow was a continuous stream if the regulating clamp was released. We used 15-gauge needles in all operations, as did Neustrup and Milowsky.[9] The effect on a blood transfusion that is running at 40 drops per minute or slower is dramatic. After the blood-Pronestyl mixture has been running 2 to 3 minutes, the rate of blood flow accelerates rapidly and reaches a maximum effect after 5 to 10 minutes. This effect is sustained as long as the mixture is continued. If more cold blood follows the blood-Pronestyl mixture, the high rate of blood flow is maintained for about 15 to 30 minutes. The rate then begins to slow and at the end of 30 to 45 minutes it decreases to about 100 drops per minute. Only rarely does the rate of blood flow return to the previous low levels of 40 or fewer drops per minute even after hours have passed since the original blood-Pronestyl mixture was administered. If an immediate effect on the rate of blood flow is desired, it is necessary to add only an extra 50 to 100 mg. of Pronestyl at the filter. Only in cases of profuse hemorrhage has it been necessary to add positive pressure to the blood transfusion setup.

It is interesting that when two bottles of blood were running simultaneously into separate extremities the addition of Pronestyl to one of them accelerated the rate of blood flow of both bottles equally. This appears to be an added advantage of Pronestyl over procaine since Neustrup and Milowsky reported that the effect of intravenous procaine in accelerating the rate of blood flow was a local one. They noted no increase in the rate of flow in transfusions running simultaneously in other extremities.

We have used Pronestyl in the recovery ward in wide-awake patients who urgently needed blood since there was no fear of toxic reactions on the central nervous system as might occur with procaine.

A small number of electrocardiograms were taken on anesthetized patients who received the blood-Pronestyl mixture. They did not reveal depression of the S or T waves, ventricular tachycardia, or intraventricular block. There was seen a lengthening of the Q-T interval. However, this effect occurred long after the effect in accelerating the rate of blood flow was established, being noted usually only after 0.5 to 1.0 Gm. of Pronestyl had been injected.

The following two case reports illustrate the use of Pronestyl to accelerate the rate of blood flow.

CASE 1.—T. D., a 58-year-old white male had a segmental pulmonary resection performed for pulmonary tuberculosis. During the thoracotomy, bleeding was more than moderate and despite early blood transfusion, replacement was rapidly falling behind blood loss. The rate of blood flow was 30 drops per minute. The addition of 0.5 Gm. Pronestyl raised the flow rate to 350 drops per minute. Blood loss was replaced, and thereafter the operation continued uneventfully.

CASE 2.—A subtotal gastrectomy was performed on a 42-year-old white male with duodenal ulcer. In the attempt to remove the ulcer at the duodenum, brisk hemorrhage was encountered. The use of cold blood prevented a fast flow rate even with the use of positive pressure in the transfusion setup. The addition of 50 mg. Pronestyl at the filter and an additional 500 mg. into the blood container resulted in an immediate and sustained effect on the rate of flow. An almost continuous stream of blood was produced, blood loss was replaced easily, and a hypotension of 80/50 mm. Hg was corrected to normotensive levels.

COMMENT

In view of the development of hypotension as a serious and frequent side effect of the intravenous use of procaine amide, the administration of approximately 400 units of a blood-Pronestyl mixture intravenously without any recurrence of hypotension is significant. Our use of Pronestyl was to prevent local venospasm associated with the use of cold blood. Since this spasmolytic effect was noted to extend to other extremities receiving blood by vein, a generalized systemic effect of Pronestyl on the circulating system, probably sympatholytic in nature, is suggested. That such a generalized effect can exist without incidence of hypotension is interesting. Although the number of electrocardiograms taken during the administration of the blood-Pronestyl mixture was too small to lend to positive statements, they did indicate that the peripheral spasmolytic effect of Pronestyl in accelerating rate of flow could not be correlated with any depressant effect on the myocardium. When electrocardiographic changes did occur, it was long after the spasmolytic effect had begun. Even with the establishment of definite electrocardiographic changes as described previously, there was no evidence of a hypotensive effect.

DISCUSSION

Research in the field of the pharmacology of procaine, especially as an intravenous agent, has led to the opinion that the drug exerts some of its clinical manifestations and side reactions by virtue of its sympatholytic effect.[10,11] Clinically, this vasodilating effect has been made use of in a variety of disorders.[12,13] Pronestyl was then introduced by Mark and associates[4] as a potent drug in the treatment of cardiac arrhythmias. However, as described here, the use of Pronestyl has been attended with alarming hypotension and, as with procaine, the etiology of this hypotension has been ascribed to two possible factors: one, a peripheral sympatholytic effect[7] and two, a direct depressant effect on the myocardium.[14,15]

Miller and associates,[7] on the basis that ventricular beats are more consistently affected by Pronestyl, suggest a sympathetic blocking action on the heart since the predominant distribution of sympathetic innervation is on ventricular foci. Such a sympatholytic effect on the myocardium would seem to explain the drug's action on cardiac arrhythmias.

Whatever the mechanism of the drug's action and its side effects, Pronestyl appears to have a sympatholytic effect which is completely unassociated with any degree of hypotension when used as described previously. This does not exclude the possibility that the hypotension may be due to a more widespread and more marked sympatholytic effect than is obtained with our method of administration.

It would also appear that the intravenous use of Pronestyl by the infusion-drip method affords control and safety above that obtained by intermittent injection.

SUMMARY

The use of Pronestyl in blood to accelerate the rate of blood flow is described.

The absence of hypotensive side effect with this method of administration is presented.

The sympatholytic effect without hypotension is discussed.

The use of Pronestyl by intravenous drip is recommended for control and safety.

SUMMARIO IN INTERLINGUA

Pronestyl (amido de procaina) esseva usate in loco de procaina pro accelerar le transfusion de sanguine in 400 casos. Le mixturas usate esseva 0,5 a 1,0 g Pronestyl per 500 cc sanguine integre. Nulle effectos hypotensive esseva observate. Nos vide le mechanismo del action de Pronestyl in un generalisate effecto sympatholytic. Il pare que le uso intravenose de Pronestyl per medio del methodo de perfusion de gutta a gutta permitte un melior controlo e un plus alte securitate que le injection intermittente.

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A NEW "PLASTER ELECTRODE" NOT REQUIRING PASTE

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IN MAKING the connection between patient and electrocardiograph two important considerations are convenience and freedom from artifact. The introduction of electrode paste[1,2] not only made possible the use of more convenient type electrodes but reduced artifacts caused by high-skin resistances. These pastes rendered obsolete the cumbersome "tub" electrodes and greatly facilitated the development of precordial lead electrocardiography. The problem changed somewhat with the shift from string to amplifier type of electrocardiograph because the high input resistance of the latter obviated the need for low-skin resistance in obtaining standardized electrocardiograms. However, this advantage was offset by the increased number of leads in the "standard electrocardiogram"; considerable time is required in obtaining the tracings. The electrode now to be described not only saves time because paste is not required but also has other technical advantages.

Four modifications of the electrode presently in use are shown in Figs. 1 to 5. That in Fig. 1 is a German silver electrode with a removable sleeve. The sleeve is made of plaster of Paris molded on a cardboard frame. The framework of the sleeve can be fashioned out of thin cardboard, Fig. 2. The rectangular hole is centered over the metal base and the flaps folded backward and glued. It will be noted that the lateral sides of the sleeve in part fold completely under to form a "track" which engages the edges of the metal base. These folded edges guide the electrode in and out of the sleeve and also exert pressure against the electrode, holding the sleeve contact more securely in place. When the glue has dried, remove the frame, coat the metal base with petrolatum, and replace. Next, prepare a mixture of calcium sulfate and sodium chloride; to 15 c.c. of water add 0.5 Gm. NaCl, then 20.0 Gm. of $CaSo_4$ and mix thoroughly. This mixture is then poured over the electrode with the rectangular hole in the paper frame facing upward. A long pin or thin wire may be used to spread the mixture evenly between sleeve and contact surface of the metal. Continue to pour the mixture until it flows out to all edges of the sleeve. Allow the mixture to solidify for about three hours. Before complete solidification occurs, scrape off any superfluous material which may have dropped over the edges during the process of pouring. When the mixture has solidified, remove the sleeve in order

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Opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the view or endorsement of the Navy Department.

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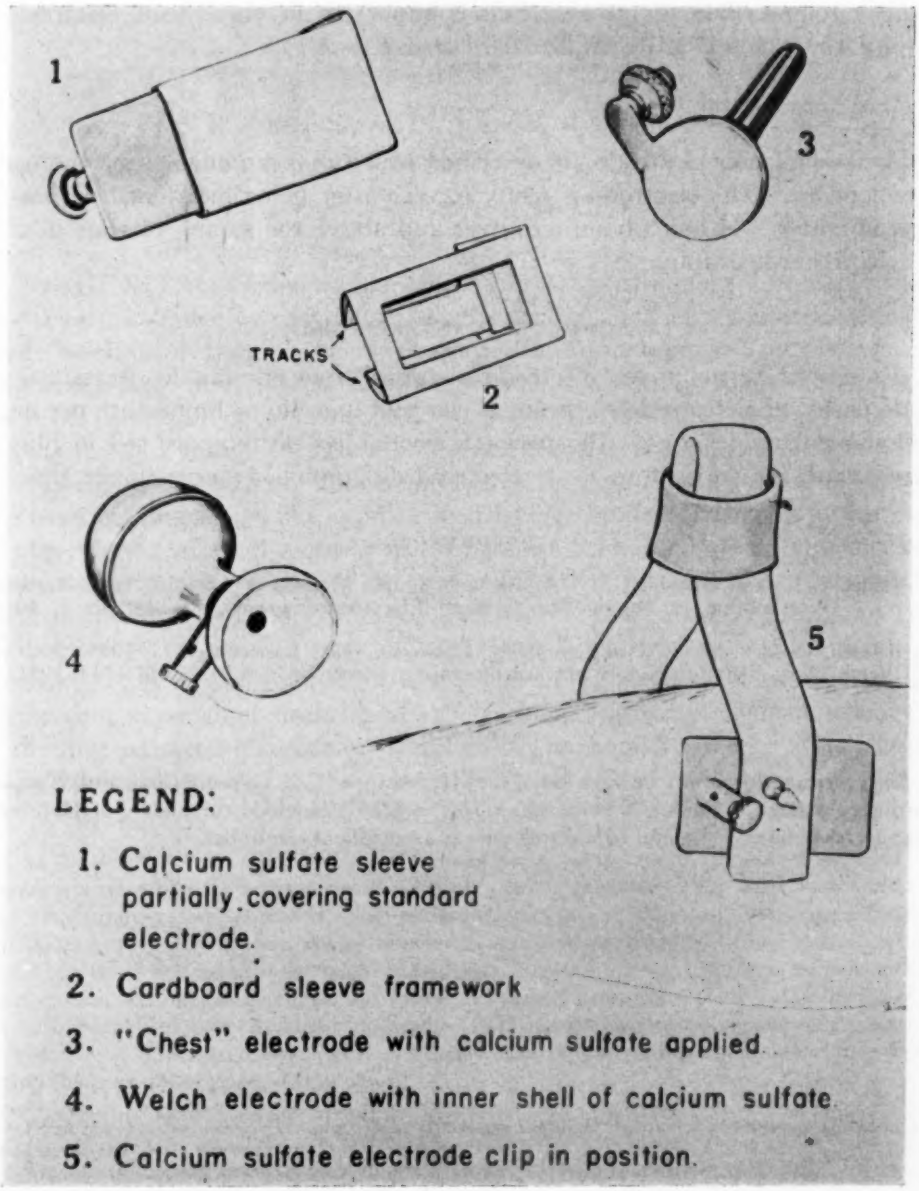
to clean petrolatum from the electrode; sleeve is readily removed by pushing back on both edges simultaneously.

Fig. 3 shows a standard "chest" electrode with the plaster applied directly to the metal, as an alternative to the "sleeve" method, and Fig. 4 shows the Welch electrode[3] similarly treated. In this instance the plaster is swirled around inside the cup so that when dried it forms a thin shell. It is necessary to scrape away the plaster ($\frac{1}{16}$ inch) near the rim smoothly, otherwise the "suction" is readily lost.



Figs. 1-5.

Fig. 5 shows a clip-on electrode, the plaster (not shown) having been applied directly to the metal. The clip was made of plastic, and a heavy rubber band can be adjusted to provide the necessary retaining friction. This electrode is comfortable for long periods of time.

All that is required before using any of these electrodes is to moisten the plaster with a few drops of water. Do not use more water than is readily absorbed. The rate of water loss will depend upon the atmospheric conditions, but a good contact can be maintained for at least an hour or more. In addition to saving time, these electrodes have the advantage of making contact with a sharply circumscribed skin area. This is important in chest lead electrocardiography where closely adjacent leads are desired.

SUMMARY

A new "plaster electrode" is described which makes unnecessary the use of contact paste. The electrode is ready for use after being moistened with a few drops of water. It has advantages over and above the saving of time in chest lead electrocardiography.

SUMMARIO IN INTERLINGUA

Es describite un nove "electrodo a gypso" que elimina le necessitate del uso de pasta. Le electrodo es preste al uso post que illo es humectate per medio de alciun guttas de aqua. Illo permitte economias de tempore sed in plus ha altere avantages super toto in le electrocardiographia a derivationes thoracic.

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ADDENDUM

Since writing this report we have found that Hydrostone (U. S. Gypsum Company) is superior to ordinary plaster of Paris. A block (2″ x 1¼″ x 5/16″) moulded completely of Hydrostone except for the embedded metal connecting post is an excellent electrode.

Clinical Reports

HEMODYNAMIC AND ANGIOCARDIOGRAPHIC OBSERVATIONS IN AN ADULT WITH PERSISTENT LEFT SUPERIOR VENA CAVA DRAINING INTO THE CORONARY SINUS AND INTERATRIAL SEPTAL DEFECT

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CONGENITAL cardiovascular anomalies are so frequently multiple that in every instance of congenital heart disease a detailed evaluation should be made to establish the presence or absence of multiple lesions. This is even more important now than previously since in many instances congenital anomalies may be corrected or improved by surgery. Accordingly, such evaluation is mandatory if a rational surgical procedure is to be determined in advance.

The case presented here was considered to have interatrial septal defect on the basis of clinical findings and routine roentgen study. During a 9-year period of observation, gradual increase in cardiac size was noted along with increasing prominence of the pulmonary arteries. In order to assess the advisability of surgical therapy, detailed evaluation utilizing cardiac catheterization and angiocardiography was carried out. The diagnosis of interatrial septal defect was confirmed, but in addition, the patient was shown to have a persistent left superior vena cava which drained into the coronary sinus. To our knowledge this is the first reported instance of diagnosis of this combination of anomalies in a living adult subject.

CASE REPORT

D.W., a 50-year-old registered nurse, first came to our attention in September, 1945. Her complaints were ease of fatigue, headache and gaseous eructations, the latter associated with emotional upsets rather than food. She had noted moderate shortness of breath on exertion since childhood, but there had been no apparent increase during adult life. She had occasional palpitation but there was no chronic cough, hemoptysis, or pedal edema. Her first knowledge of her heart disease was in 1931 when she was told that she had a murmur. The patient has been continuously employed as a registered nurse since 1935 except for two periods of pregnancy. She delivered normal infants, a girl in 1937 and a boy in 1941, without significant cardiac symptoms during the prenatal or post-partum period.

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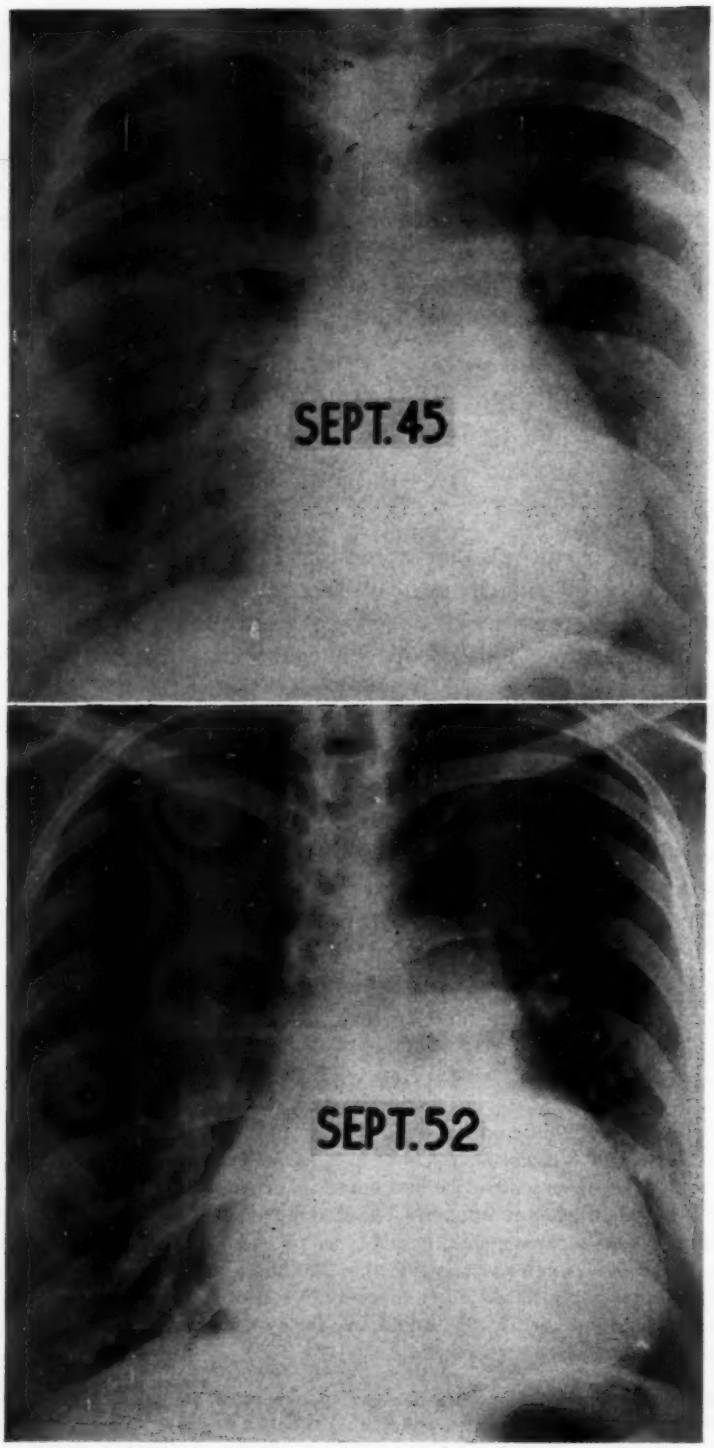
*Resident in Medicine.

A.



B.

Fig. 1.—*A*, Posteroanterior roentgenogram of chest on September 17, 1945. Frontal plane-surface area measures 150.8 sq. cm. *B*, Posteroanterior roentgenogram of chest on September 26, 1952. Note marked increase in heart size and increased prominence of pulmonary arteries. Frontal plane-surface area measures 169 sq. cm.

The physical examination in 1945 showed the patient to be unusually well developed and well nourished: height, 68 inches; weight, 148 pounds; blood pressure, 130/85 mm. Hg; vital capacity, 2.5 liters or 75 per cent normal. There was no chest deformity. The heart was enlarged and hyperdynamic, and the left border was just inside the anterior axillary line. The rhythm was regular except for occasional premature beats. A short systolic thrill and a diastolic shock were noted in the pulmonic area, the former associated with a coarse basal systolic murmur. A faint apical systolic murmur was present, but there were no diastolic murmurs. The remainder of the physical examination was negative except for an external strabismus of the left eye.

During the interval from 1945 to 1953 the patient was seen infrequently with noncardiac complaints. X-ray examination of the chest in November, 1953, showed a cardiac surface area of 142 per cent of normal as compared with 120 per cent in 1945 (Fig. 1). The systolic thrill, systolic murmurs, and accentuated P_2 were essentially unchanged from those of 1945. Fluroscopic examination showed a striking hilar dance in addition to the cardiomegaly and dilated pulmonary arteries. Blood pressure was 140/75 and 150/60 mm. Hg before and after exercise, respectively. Electrocardiograms taken in 1945 and in 1953 are presented in Fig. 2.

Angiocardiographic and right heart catheterization studies: An initial angiocardiogram was done using the antecubital vein of the right arm. Fig. 3 shows a right superior vena cava of small caliber, with an atypical entrance into the right auricle. The pulmonary artery was distinctly opacified in gradually diminishing degree for the remainder of the 8-second period.

The following week, right heart catheterization was attempted using the left antecubital vein. The catheter passed with ease through the axillary and subclavian veins, but, continued manipulation failed to cause the catheter to enter a left innominate vein. Instead the catheter persisted in coursing down the left cardiac border. The catheter tip was advanced down along the posterior surface of the heart but could not be directed into the ventricle, Fig. 4,*B*. Pressure curves obtained at different levels in this anomalous venous channel are shown in Fig. 5. The angiocardiogram was subsequently repeated from the left side. The anatomic relations of the persistent left superior vena cava are demonstrated in Fig. 6.

On December 15, 1953, the second catheterization was done using a right arm vein. It was possible to pass the catheter into the right and left auricles, right ventricle and right pulmonary artery (Fig. 4,*A*). The hemodynamic data obtained thrcugh the two superior venae cavae are listed in Tables I and II, respectively. The clinical impression of a left-to-right shunt at the level of the auricle was confirmed by the increased oxygen content in the right auricle, as compared with the superior vena cava. The left auricle was entered through the defect as evidenced by the position of the catheter, fluoroscopically, and the extremely high oxygen saturation (96 per cent) obtained from this site. Anomalous pulmonary venous drainage into caval systems appears

TABLE I. HEMODYNAMIC OBSERVATIONS OBTAINED VIA LEFT SUPERIOR VENA CAVA AND BRACHIAL ARTERY

	SITE	REST	EXERCISE
Oxygen saturation per cent	Superior vena cava	61	
	Coronary sinus	58	54
	Brachial artery	94	88
Oxygen consumption, c.c./min./BSA		146	366
Systemic flow, L./min./BSA		2.42	5.05

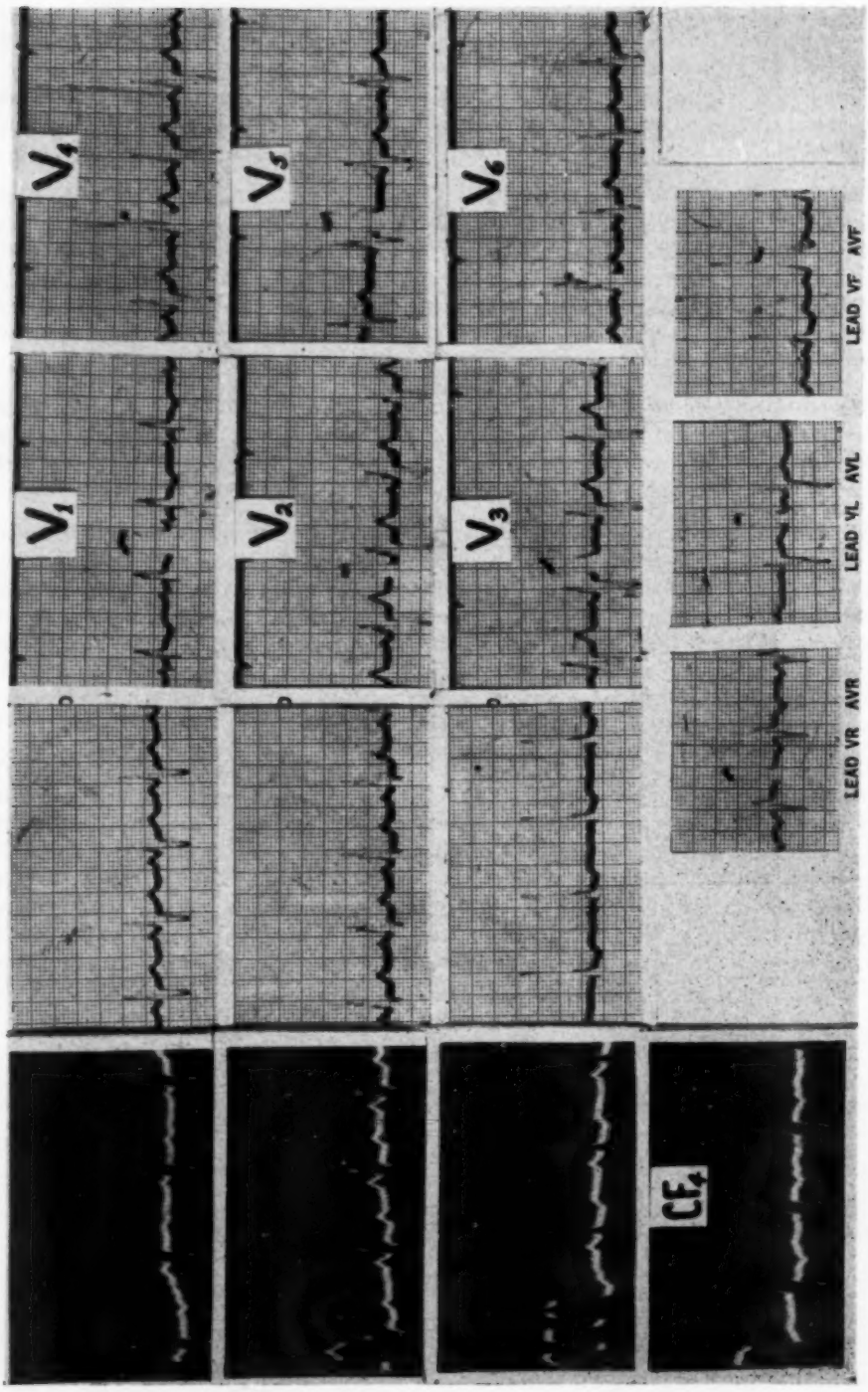
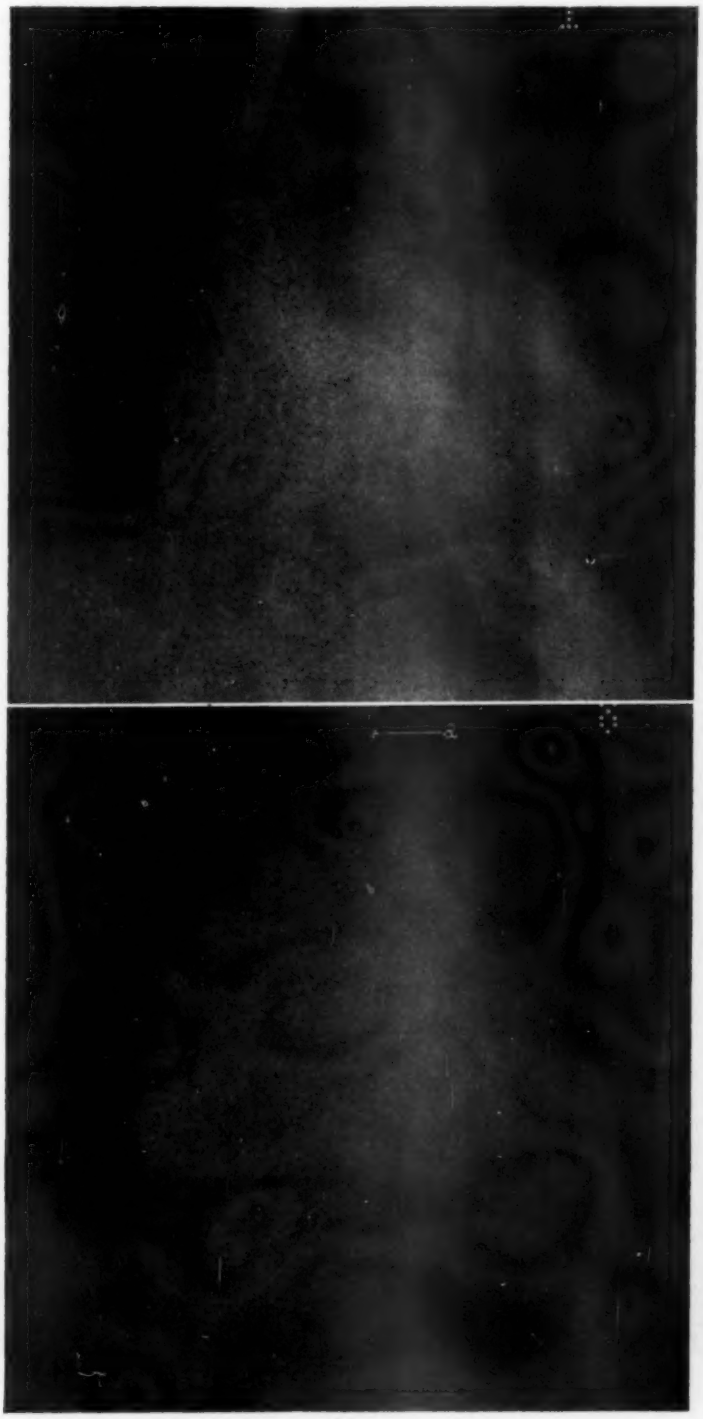


Fig. 2.—Comparison of electrocardiograms taken in 1945 and 1954.

A.



B.

Fig. 3.—*A*, Angiocardiogram at one second. Note size and shape of superior vena cava. *B*, Angiocardiogram at eight seconds. Note that there is still opacification of right side of heart and the density of pulmonary arteries and right side of heart is about the same as it was at two seconds when right side of heart was first filled with the dye. Aorta is seen opacified at upper aspect of film (*a*).

to be excluded by the comparative oxygen contents of the caval and right auricular blood samples. A distinct fall in arterial oxygen saturation was noted during the period of leg exercise probably indicating some degree of right-to-left shunt during some phase of the cardiac cycle. The work of

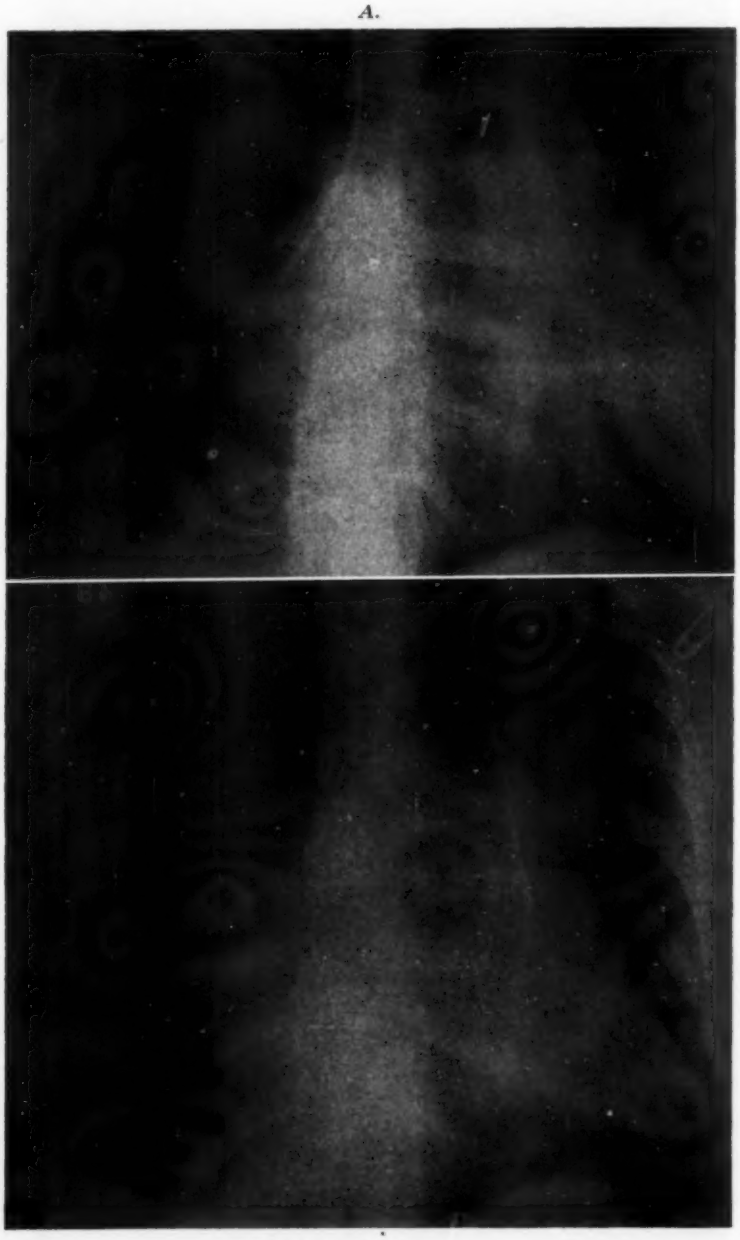


Fig. 4.—*A*, Catheter inserted into right basilic vein is seen extending through right superior vena cava into right atrium. *B*, Catheter inserted in left basilic vein is seen following the course of the persistent left superior vena cava.

the left ventricle against pressure was normal, while that of the right ventricle was greater than the left and about six times normal. It is of significance, however, that the pulmonary arterial resistance is still within normal limits (Table II).

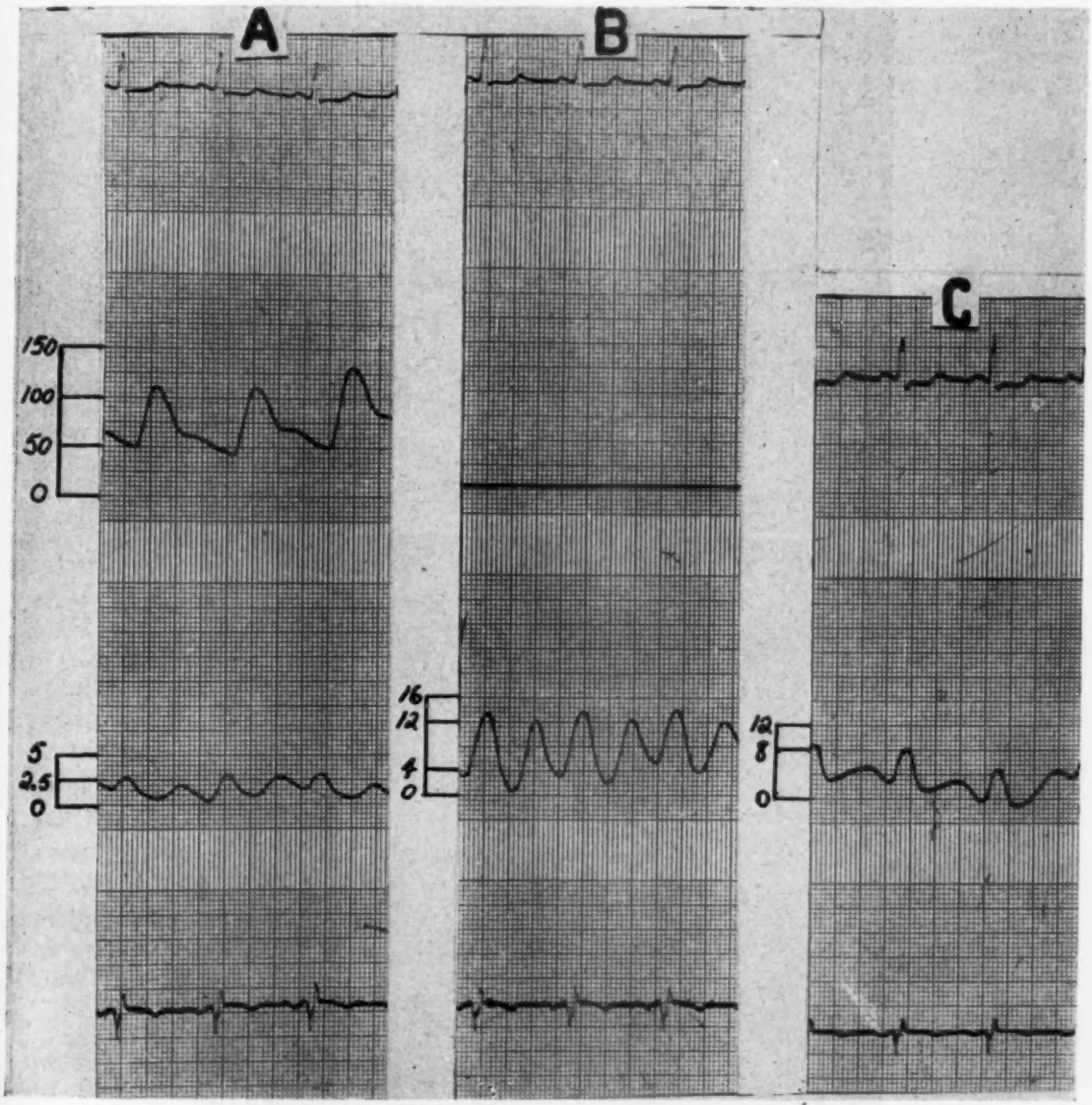
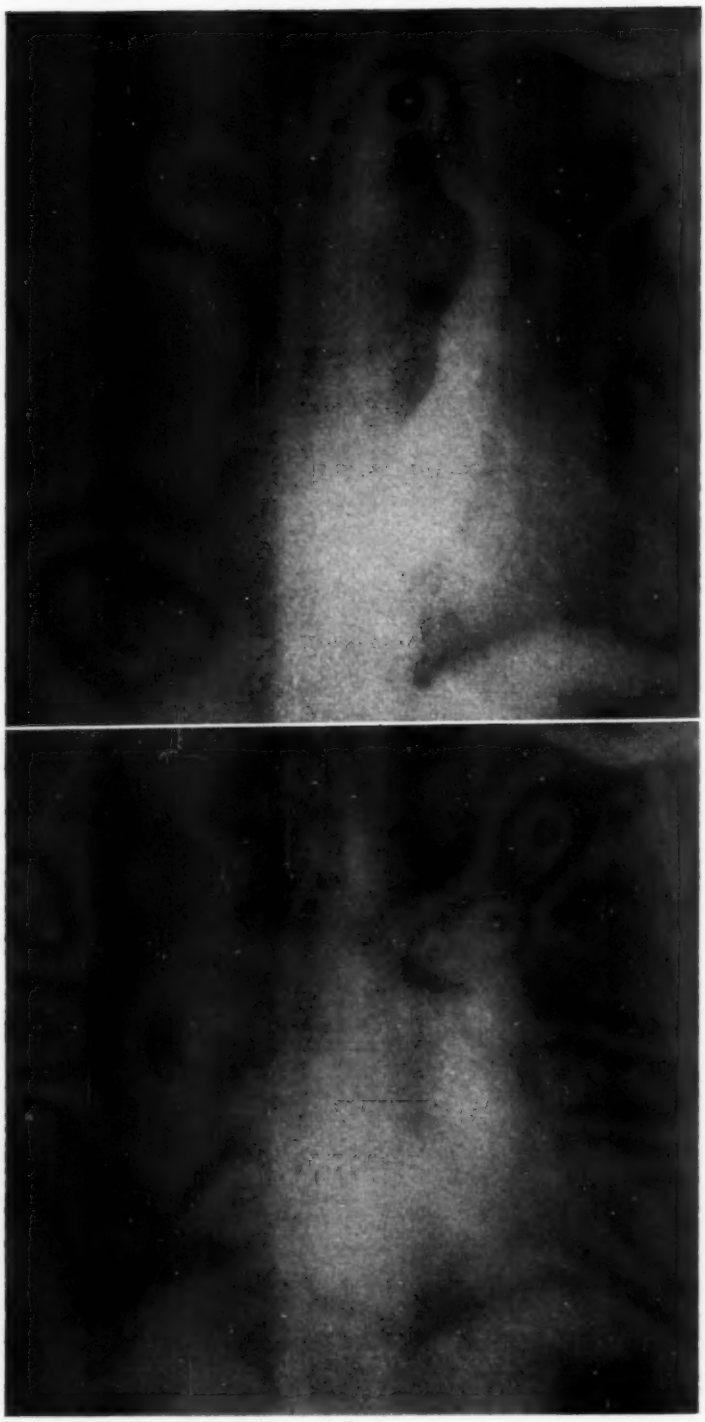


Fig. 5.—Pressure curves from brachial artery and from catheter through left superior vena cava. *A*, Brachial artery and distal end of left superior vena cava or coronary sinus. *B*, Coronary sinus via left superior vena cava. *C*, Upper end of left superior vena cava.

A.



B.

Fig. 6.—*A*, Angiocardiogram following injection of dye from left side through left basilic vein. Film made at 1½ seconds following injection. Note persistent left superior vena cava. *B*, At 4 seconds right ventricle and pulmonary arteries densely opacified. Note indentation on superior vena cava produced by left pulmonary artery.

TABLE II. HEMODYNAMIC OBSERVATIONS OBTAINED VIA RIGHT SUPERIOR VENA CAVA AND BRACHIAL ARTERY

	SUPERIOR VENA CAVA	RIGHT AURICLE	RIGHT VENTRICLE	PULMONARY ARTERY	BRACHIAL ARTERY	LEFT AURICLE
Blood oxygen saturation (%)	68	82	82	86	94	96
Blood pressure mm. Hg		(10)		41/23 (32)	144/70 (95)	(14)

	BLOOD FLOW L./MIN./BSA	HEART RATE	STROKE VOLUME C.C. MIN.	RESISTANCE DYNES/ SEC./CM.$^{-5}$	VENTRICULAR WORK AGAINST PRESSURE KG.-M./MIN./BSA	
					RIGHT*	LEFT
Pulmonary artery	12.4	76	307	110	3.914	
Systemic	3.1	80	72	1320		3.60
Shunt (Left-to-right auricle)	9.3					

*Normal range 0.4 to 1.2 Kg./min./M^2
( ) = Mean Pressure

DISCUSSION

Persistent left superior vena cava draining into the coronary sinus is more readily understood by a review of the embryologic development of the great veins.[1] Fig. 7,*A* shows the venous pattern in a six-week embryo. Note the paired precardinal and postcardinal veins draining into the paired common cardinal veins. The right and left common cardinal veins drain into the right and left horns of the sinus venosus, respectively. At 8 weeks, Fig. 7,*B*, an anastomosis becomes the left innominate vein. Soon after this development the terminal end of the left precardinal vein loses connection with the left common cardinal vein, the former persisting as the highest intercostal vein and the latter becoming the oblique vein of the left auricle which drains into the coronary sinus (Fig. 7,*C*).

Occasionally, evolution of the venous system may stop at any of the intermediate stages of development. In the case presented here it is our impression that the paired precardinal veins persisted as in the six-week embryo resulting in a persistent left superior vena cava draining into the coronary sinus, and absence of the left innominate vein.

A tabulation of the anomalies in cases of persistent left superior vena cava, observed in the cadaver, has been made by McCotter[2] and by McManus.[3] A modification of their tabulations is listed here.

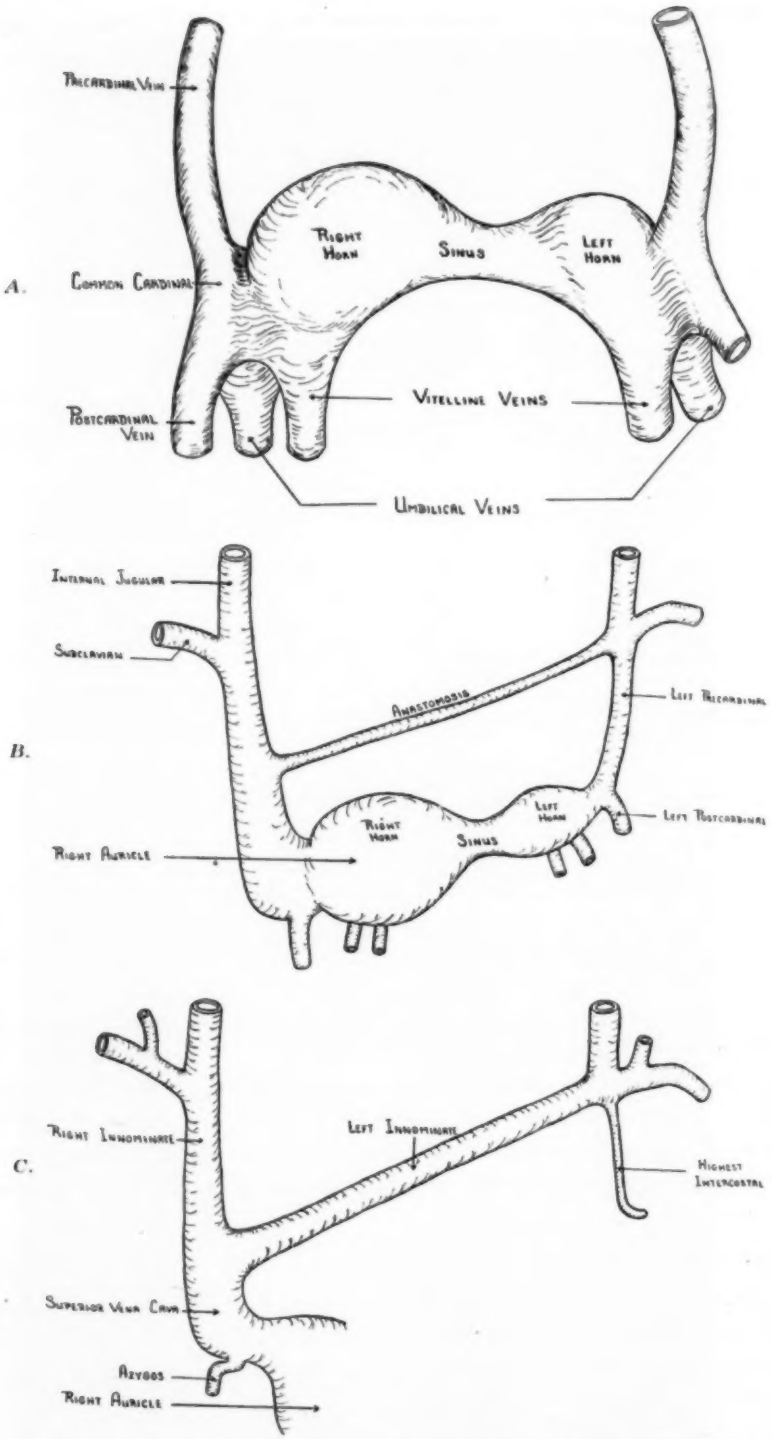


Fig. 7.—Embryologic development of large venous channels draining into superior vena cava on the right. *A*, Six weeks; *B*, Eight weeks; *C*, Mature embryo.

TABULATION OF TYPES OF PERSISTENT LEFT SUPERIOR VENA CAVA

I. Persistent left superior vena cava without anomaly of the pulmonary veins
   A. Associated with right superior vena cava
      1. With drainage into coronary sinus
         a. With cross anastomosis (innominate vein)
         b. Without cross anastomosis (innominate vein)
      2. Without drainage into the coronary sinus
         a. Drainage into right auricle via innominate vein and right superior vena cava
         b. Drainage into the left auricle
   B. Without associated right superior vena cava
II. Persistent left superior vena cava draining the pulmonary veins
   A. Drainage of pulmonary and systemic veins into the right auricle
      1. Via left innominate vein and right superior vena cava
      2. Via the coronary sinus
   B. Drainage of pulmonary and systemic veins into left auricle
   C. Drainage of pulmonary veins alone into right atrium through coronary sinus via short left superior vena cava

A bibliography of the older literature is given by Chouke.[4] It is of interest that some of the reported cadaver cases of left superior vena cava are associated with interatrial septal defect[2] as in the case presented here, and in some, patency of the ductus arteriosus also.[3]

The persistent left superior vena cava may be of little physiologic significance so long as it drains only systemic venous blood into the right auricle.[5] In such cases it may be of importance in thoracic surgery. On the other hand the anomaly may be of considerable clinical importance when it drains systemic and pulmonary venous blood into the right or left auricle. If the total pulmonary venous drainage is into the right auricle via the left superior vena cava, symptoms may be severe.[6] Neptune and associates,[7] have indicated that correction of such defects could be achieved by section of the persistent left superior vena cava and implantation of the proximal end into the left auricle. In the case presented here the left superior vena cava draining into the coronary sinus appears to cause no physiologic abnormality.

A decision concerning surgical therapy in this patient was the primary purpose of the detailed study. It is well known that many patients with significant interatrial septal defects may have a long life span.[8] This patient is already 50 years of age, has two children, and is gainfully employed. The oldest patient[9] in our series was a woman, aged 70. In view of the potential longevity in these patients and the fact that to date surgical therapy is not entirely satisfactory, considerable caution must be used in making a decision for surgical intervention. Although patients with significant interatrial septal defects may have mild exertional dyspnea, palpitation, and precordial pain for many years, it appears that the life span will be shortened only with the appearance of greatly increased dyspnea and the early signs of congestive heart failure.[8] With the distinctly increasing cardiomegaly we believe that this patient is nearing this crucial stage. In view of the large left-to-right shunt and the fact that she apparently has little pulmonary arteriolar sclerosis as judged by the normal pulmonary resistance, it appears that surgical therapy should be advised for this patient now. To date this patient has not been willing to have surgical repair attempted.

SUMMARY

1. A case is reported which shows a persistent left superior vena cava draining into the coronary sinus and associated with a large interatrial septal defect in a woman, aged 50 years.

2. The embryologic basis of anomalies of the superior vena cava is reviewed, and a classification of the types of persistent left superior vena cava is presented.

3. The patient was shown to have a large left-to-right shunt and increasing cardiomegaly but normal pulmonary arterial resistance.

4. Although definitive criteria for surgical therapy of interatrial septal defects in adults are not yet crystallized, we believe the patient is approaching the critical stage when heart failure is imminent and, therefore, recommend surgical intervention.

SUMMARIO IN INTERLINGUA

1. Es reportate le caso de un femina de 50 annos de etate con drainage de un persistente sinistre vena cave superior a in le sino coronari in association con un grande defecto interatrial.

2. Secundo nostre informationes isto es le prime publicate reporto de iste combination de anomalias in un vivente subjecto adulte. A causa del frequentia de multiple congenite anomalias cardiovascular, le evalutation de cata varietate es importante, specialmente in nostre tempore ubi multe congenite anomalias cardiac pote devenir candidatos de chirurgia corrective.

3. Es presentate un revista del bases embryologic del anomalias del vena cave superior e un classification del typos de persistente sinistre vena cave superior. Le caso de nostre patiente es characterisate per un grande derivation ab le sinistra verso le dextera e progressive megalocardia sed un resistentia normal del arteria pulmonar.

4. Ben que definitive criterios pro le therapia chirurgic de defectos del septo interatrial es nondum crystallisate, nos crede que le patiente approcha le stadio critic ubi dysfunctionamento del corde es imminente e ha recommendate intervention chirurgic.

Acknowledgment is made of the technical assistance of Audrey Fairley, Clarence Carter, Thelma Blakey, and Mary Brooks.

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ANEURYSM OF THE THORACIC AORTA: AN UNUSUAL PRESENTATION

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ANEURYSMS presenting as superficial swellings are frequently seen in medical practice in Singapore. The commonest point of origin is the ascending aorta with the tumor appearing parasternally in the second or third right intercostal space. Other areas in which superficial aneurysmal swellings have been seen are the front of the neck, the axillae, the popliteal spaces, the epigastrium, and the back of the chest adjacent to the spine. While on radiologic or postmortem examination multiple aneurysmal sacs have been noted involving either aortic arch alone or aortic arch and abdominal aorta in the region of the celiac plexus, in local experience presentation of aneurysms as multiple subcutaneous lumps has not been previously recorded.

In a country where all forms of cardiovascular syphilis are frequently seen, the clinical presentation of this case of aneurysm of the ascending aorta is considered unusual and worth recording.

CASE REPORT

S.H.K., a male Chinese aged 57 years, was admitted on Feb. 10, 1950, to the General Hospital, Singapore, complaining of lumps on the front of the chest, breathlessness, and swelling of the feet. He had stopped working as a dockyard laborer some five years previously because he felt he was getting on in years and his children were able to support him.

He felt quite well until three and one-half years before admission when a throbbing kind of pain developed behind the sternum. This pain appeared at irregular times without any definite relation to exercise and lasted for one or two hours. During the following eight months, the attacks of pain grew gradually worse but were not severe enough to restrict his normal activities or disturb his sleep.

Two years and ten months prior to admission, he noticed the appearance of two small lumps, one on either side of the lower end of the sternum. Each was about the size of the tip of a finger, did not pulsate, and was not painful. With their appearance, the retrosternal pain completely disappeared and did not return. The lumps gradually increased in size but their presence did not in any way restrict his activities. However, during the last three months, he developed breathlessness on exertion. This progressed steadily so that for the past week he had been unable to walk and could only sleep when propped up in bed; swelling of both feet was then noted. The normal frequency of micturition was not altered but the volume of urine was decreased. Appetite remained good.

Twenty-five years previously, he had developed a penile sore and urethral discharge after exposure to venereal disease. He received local treatment but no injections. His wife had two abortions. Three sons and one daughter were living and well.

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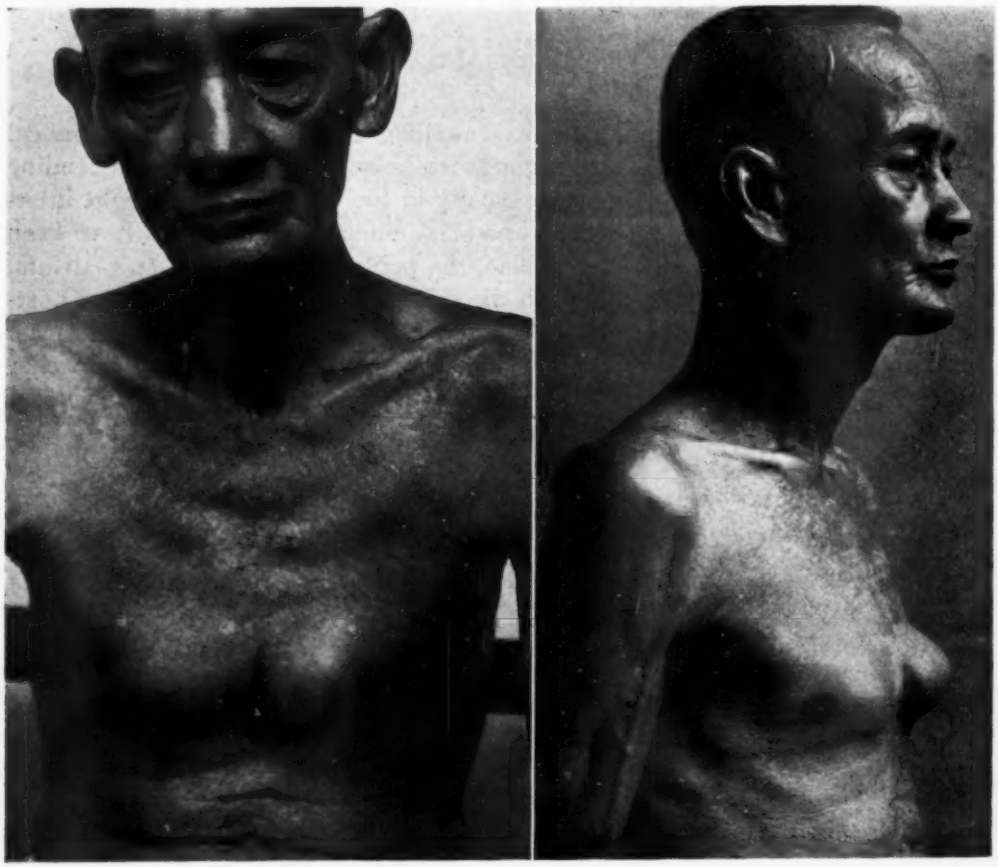
Physical examination, on admission, revealed a thin elderly-looking man who was breathless unless propped up in bed. The respiratory rate was 28 per minute, the temperature was normal, and the pulse rate was 96 per minute. There was no cyanosis or clubbing of fingers or toes. The cervical veins were engorged up to the angle of the jaw even when the patient was propped up to an angle of ninety degrees. Visible pulsations of the large arteries in the neck, arms, and groins were noted. The radial pulses felt equal and were collapsing in character; the blood pressure was 130 mm. Hg systolic and 34 mm. Hg diastolic and equal on both sides. There was pitting edema of the feet and legs.



A. *B.*

Fig. 1.—A and B, Photographs of patient.

Three smooth swellings were seen adjoining the lateral borders of the lower third of the sternum (Fig. 1, *A* and *B*). The first and largest was a rounded swelling 9 cm. by 9 cm. occupying the fourth, fifth, and sixth left intercostal spaces and projecting forward for 4 cm. Separated from it by the body of the lower end of the sternum was the second lump, also rounded but slightly smaller and measuring 7 cm. by 6 cm.; it occupied the fifth and sixth right intercostal spaces parasternally and projected forward for 3 cm. These two swellings were on a level with the nipples which were in the fifth intercostal space on either side. The third lump was a small rounded swelling about 2 cm. by 2 cm. appearing as a fullness of the third right intercostal space parasternally. These swellings showed visible pulsation which was distinctly expansile in character denoting their vascular origin. There was no discoloration or inflammation of the overlying skin. No thrills were felt over the swellings or over the rest of the precordium. On

auscultation a soft systolic and a blowing diastolic murmur of Grade 2 intensity were heard over each lump. The murmurs were those characteristic of aortic insufficiency.

The apex beat was distinctly felt 13.5 cm. from the mid-line in the sixth left intercostal space and was forceful, rapid, and regular. In the aortic area the first sound was replaced by a soft systolic murmur, Grade 3 in intensity, conducted into the vessels of the neck. The second sound was replaced by a blowing diastolic murmur which was conducted down the right and left sides of the sternum to the apex; it was heard loudest (Grade 3) in the third intercostal space just to the left of the sternum. In the pulmonary and mitral areas both sounds were replaced by soft systolic and diastolic murmurs having the same quality as those in the aortic area.

It was noted on examination of the lungs that there was impaired resonance with diminished breath sounds and crepitations over both bases. The liver was palpable 2 cm. below the costal margin; the spleen was not felt. There was a penile scar and the inguinal lymph nodes were palpable. No abnormality was found in the central nervous system.

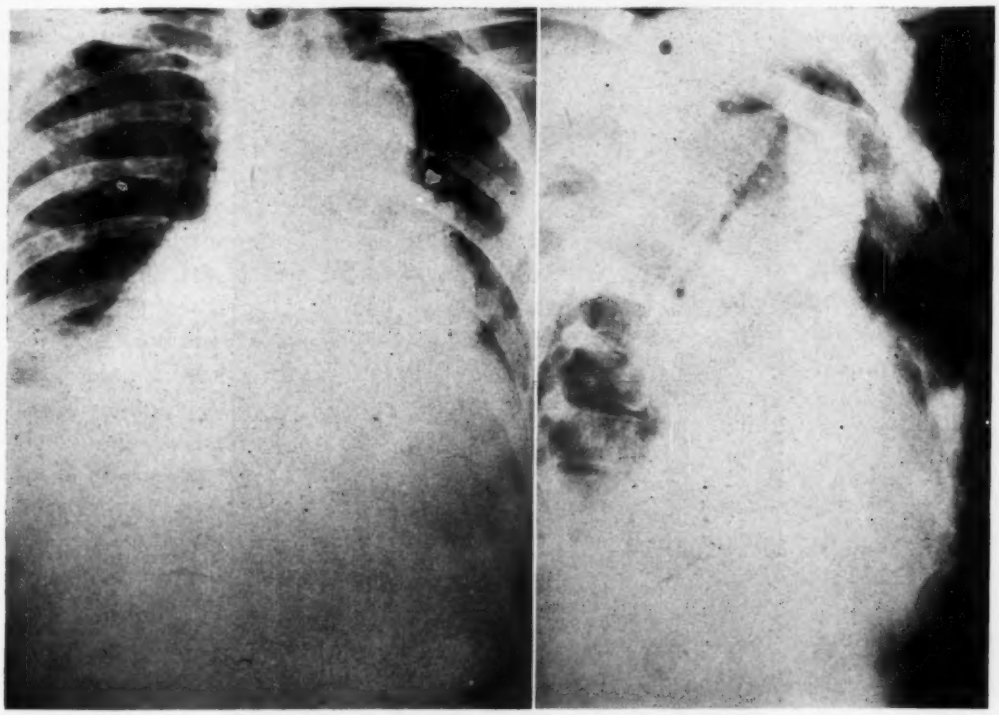


Fig. 2. Fig. 3.

Fig. 2.—Chest roentgenogram, posteroanterior view.

Fig. 3.—Chest roentgenogram, right oblique view.

Laboratory investigations revealed a red cell count of 3,850,000 cells per cubic millimeter with a hemoglobin content of 60 per cent (8.9 grams). The leukocytes numbered 10,300 /cu. mm.; the differential count was normal. The blood urea was 49 mg. /100 ml., and there was a trace of albumin in the urine but no casts or cells were seen in the sediment. The electrocardiogram was normal. The blood Kahn test was positive (444).

Radiologic examination revealed a heart enlarged both to the right and left together with slight widening of the aortic arch; the lumps appeared to merge with the cardiac shadow and could not be delineated from it (Figs. 2 and 3). The retrocardiac space was obscured and the esophagus displaced slightly backwards. Pulsations of the heart and aorta were moderately vigorous. A small pleural effusion was present on the right side. There was no erosion of the ribs.

The patient's condition deteriorated, and he died four days after admission.

Fig. 4.

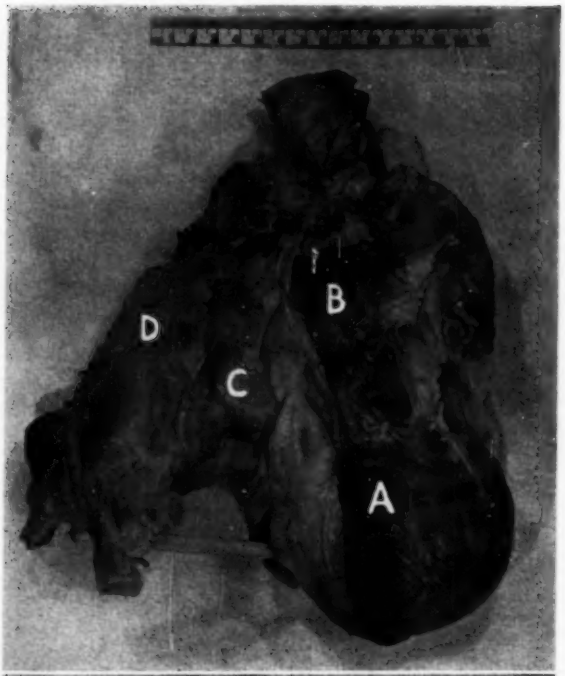


Fig. 5.

Fig. 4.—Photograph showing left ventricle (*A*), opening of aneurysmal sac (*B*), the sac itself (*C*), and the sternum (*D*).

Fig. 5.—Photograph of sac opened from the back showing posterior surface of the sternum and the three subsidiary sacs *A*, *B*, *C*.

At *necropsy* the heart was displaced to the left and posteriorly by an aneurysm of the ascending aorta. The left ventricle was dilated and showed slight hypertrophy, the myocardium measuring 1.4 cm. in thickness. The aortic valves were a little thickened but showed no widening of the commissures; the other valves were normal. No atheromatous changes were seen in the coronary arteries.

The aortic ring and arch were dilated, and the intima was wrinkled with pitted scars. From the ascending aorta a rounded opening 5.5 cm. wide led into a saccular aneurysm which dipped downward behind the sternum in front of the heart (Figs. 4 and 5). The sac measured 12 by 10 by 6 cm. and did not contain any thrombi; its wall was fairly smooth. There were three prolongations of the sac through the chest wall along both sides of the sternum, one through the fourth left intercostal space, another through the fifth right intercostal space, and one through the third right intercostal space. These smaller sacs had openings measuring 1 cm., 3 cm., and 2 cm., respectively, in diameter at their points of origin from the main sac. Passing through these noted intercostal spaces they had formed larger tumors on the chest wall. The rest of the aorta showed atheromatous changes.

The right pleural cavity contained ten ounces of clear yellow fluid, and the lungs were generally congested. The liver was of normal size but indurated. The rest of the organs were normal.

COMMENT

There was no doubt on clinical examination that one was dealing with a case of cardiovascular syphilis and that the tumors on the chest wall were aneurysmal swellings, but their site of origin was more difficult to determine. The large size of the swellings, their gradual evolvement and long duration did not appear compatible with a diagnosis of cardiac aneurysm secondary to myocardial infarction, and they were therefore considered to arise from the base of the aorta producing at the same time dilatation of the aortic ring with resultant aortic insufficiency. At necropsy the heart was displaced backward and to the left by a large saccular aneurysm of the ascending aorta which had descended in front of the heart and pointed on either side of the lower end of the sternum. The remarkable discrepancy between the gross physical signs and the minimal symptoms (except at the termination) should be noted.

SUMMARY

A case of aortic aneurysm which was present as multiple lumps over the precordium is reported.

SUMMARIO IN INTERLINGUA

Es reportate ab Singapur le caso de un travaliator chinese con aneurysma aortic manifeste per le presentia de multiple grumos supra le precordio. Le examine clinic permitteva nulle dubito de que il se tractava de un caso de syphilis cardiovascular. Le disponibile datos non pareva compatibile con un diagnose de aneurysma cardiac secundari a infarction myocardial. Nos concludeva que le grumos habeva lor origine al base del aorta, que le processo de lor formation habeva causate simultaneemente un dilatation del anulo aortic, e que isto habeva resultate in insufficientia aortic. Le examine necroptic revelava que le corde esseva displaciate a retro e verso le sinistra per un grande aneurysma saccular del aorta ascendente. Iste aneurysma habeva penetrate a basso al fronte del corde e se extendeva verso ambe lateres del extremitate inferior del sterno.

My thanks are due to Dr. K. Shanmugaratnam for performing the necropsy of this case.

NEUROGENIC SARCOMA IN THE HEART

KAI DAMMERT, M.D., GUSTAF ELFVING, M.D., AND
PENTTI I. HALONEN, M.D., F.C.C.P.

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PRIMARY tumors of the heart and pericardium are rare. The monograph on cardiac tumors by Mahaim[1] mentions 329 primary tumors of the heart and 84 of the pericardium. Among the former were 87 malignant sarcomas. Prichard[2] reports that a total of 113 sarcomas of the heart have been published. The histologic picture of this neoplasm varies greatly, as is seen from the list published by Whorton[3] of the pathologico-anatomic diagnoses in 100 cases of sarcoma of the heart, as follows:

Round-cell sarcoma	18
Spindle-cell sarcoma	18
Pleomorphic-sarcoma	11
Rhabdomyosarcoma	9
Fibrosarcoma	8
Myxosarcoma	6
Leiomyosarcoma	5
Idiopathic hemorrhagic sarcoma (Kaposi disease)	5
Giant-cell sarcoma	4
Reticulum-cell sarcoma	3
Lymphosarcoma	2
Fibromyosarcoma	2
Hemangioendothelioma	2
Embryonic sarcoma	1
Cavernous angiosarcoma	1
Spindle-cell or myxosarcoma	1
Spindle-cell and myxosarcoma	1
Cavernous angiosarcoma and spindle-cell sarcoma	1
Endothelioma	1
Mesoblastoma	1

The topography of the cardiac region and the nature of the sarcomatous growth frequently cause difficulties in differentiating sarcomas of the heart and pericardium extending into the mediastinum from mediastinal sarcomas involving the pericardium or the heart. Furthermore, as sarcomas of the heart and pericardium and those of the mediastinum may be of the same type histologically, the difficulty of differentiation is readily understood. Whorton[3] stated that primary tumors of the heart do not form an exact entity but many of them possess, nevertheless, similar clinical and pathologic features. Jucker[4] considered that primary tumors of the pericardium and neoplasms of the heart wall extending within

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the pericardium belong to the same group. Attention has also been drawn to the circumstance that a malignant growth in the heart is more frequently located in the right half of the heart, whereas the left half is more commonly the site of benign tumors.

The literature contains surprisingly few references to neurogenic tumors that invade the heart or the pericardium. Kienböck and Redlich[5] described a sarcomatous tumor arising in the vagus nerve and extending to the pericardium in a female patient 39 years of age with neurofibromatosis. The same case has later been referred to by Hamperl[6], Kienböck and Rösler[7] and Kienböck and Weiss.[8] A neuroblastoma originating in the pericardium was reported by Jucker, who regrettably omitted to give a more detailed histopathologic description of the neoplasm. The case of Keller and Callander[9] should also be mentioned, since in this case a neurofibroma originating in the phrenic nerve was found in the pericardial pleura. The frequent occurrence of neurogenic neoplasms in the mediastinum, specifically pointed out by Schlumberger,[10] should be noted in this connection.

We have recently had occasion to diagnose a case of malignant neurogenic tumor involving the heart and pericardium, and we consider that a detailed report of this case may be desirable.

CASE REPORT

The patient was a bricklayer 52 years of age, previously in good health. Since early 1952, there had been precordial pain on exertion. In March, 1953, he injured his chest on a log. In less than two weeks there was an onset of this pain also at rest, and the patient became incapable of work. At about this time dyspnea and cyanosis of the lips also set in. When the dyspnea increased to such an extent that he was unable to be in an upright position, and the chest pain became aggravated he sought the nearest rural hospital.

The patient was found to be severly dyspneic and slightly cyanotic, but there was no edema. Dullness over the heart was greatly increased, and all the extremity leads in the electrocardiogram showed pathologically low waves. Sedimentation rate varied between 15 and 40 mm./hr. There was no anemia. Urinalysis was negative for sugar and albumin. The pericardial cavity contained a large amount of fluid which was withdrawn by puncture a number of times, 750 to 1,220 c.c. at a time. It was hemorrhagic and contained no bacteria or tumor cells. As no improvement was obtained in the patient's condition he was referred to the First University Surgical Clinic in Helsinki.

On admission on May 21, the patient was in a poor physical condition. He complained of a pressure pain in the chest. His lips were cyanotic and the small veins of the neck and face were dilated. No edema was present nor were any enlarged lymph nodes palpable. The neurologic examination did not reveal abnormal features. No special findings were made in the digestive organs except in the liver, which was enlarged by one fingerbreadth, smooth and tender. Observation of the respiratory organs indicated that the patient was severely dyspneic at rest and fine bubbling râles were heard over the lower portions of both lungs. The radial artery was smooth and the pulse regular at about 75 per min. The blood pressure readings were 110/60 mm. Hg. There were no pulsations in the region of the heart and the apical beat was neither visible nor palpable. The relative dullness over the heart had extended both to the right and to the left by about three fingerbreadths. The heart sounds were barely audible. Some of the data in the laboratory tests were as follows: blood. Wassermann and Kahn negative; sedimentation rate, 35 mm./hr; hemoglobin, 12.8 grams; and the clotting and bleeding times were within normal limits. Nonprotein nitrogen was 50 mg. per cent, proteins 5.7 gram and NaCl 526 mg. per 100 cu. cm. The alkali reserve was 59 per cent by volume. Urinalysis revealed no sugar or albumin.

The electrocardiogram had sinus rhythm. All extremity leads showed low waves, but otherwise there were no abnormalities.

The thorax roentgenogram revealed accumulation of fluid in the left pleura; the heart shadow was considerably enlarged in all directions and pulsations were practically absent. In tomography (Fig. 1) a large amount of fluid was seen in the pericardium; the heart, about normal in size, was seen in the center of the fluid. No tumor shadows were discerned.

Fig. 1.—X-ray picture showing marked enlargement of the heart in both directions.

Course: A pericardial puncture was performed immediately on admission of the patient. The puncture fluid was fairly clear but hemorrhagic. Bacterial staining did not reveal any bacteria. Bacterial cultures were negative. No tumor cells were found. In view of imminent cardiac tamponade six punctures were made and 200 to 800 c.c. of fluid were withdrawn each time. The patient's condition was very grave throughout, and he died on June 7, 1953.

Clinically the case was regarded as a malignant primary tumor of the heart, most probably a sarcoma.

Autopsy: The pericardium was very greatly increased in size. The left lung, compressed to about fist-size, was lying at the left margin of the mediastinum. The right lung was voluminous and hydropic. The pleurae of both lungs contained about one liter of serous fluid. On the outer surface and in the parenchyma of both lungs there were a large number of protruding, gray, homogeneous nodules about 1 cm. in diameter. Caudal to the bronchial bifurcation was a larger conglomeration of similar tumor tissue, which partially infiltrated the median surface of the right lower lobe ventral to the hilus and partially extended anteriorly into the pericardial cavity. The transverse sinus was filled with pale gray tumor tissue. In the inferior portion of the vena cava cranialis there was an infiltration which grew into the lumen. Above this infiltration the vein was thrombosed and occluded as far as the jugular veins.

The enlarged pericardial cavity was filled with a fibrinous substance and a brownish fluid. The heart was approximately normal in size. The heart, the loose fibrinous mass, and the fluid were removed from the pericardial cavity, exposing on the inner surface of the pericardium small, firm, partly hemorrhagic tumor nodules of varying size. Similar nodules were present also on

the outer surface of the pericardium, and they appeared to be very profuse in the subepicardial tissue. On section the heart muscle was of a variegated red and brown color, almost evenly thickened and cloudy. The ascending part of the conus pulmonalis was narrowed due to an intramural, typically fasciculated tumor growth. The internal membranes of the heart were pale and smooth. The valves and coronary vessels were free. No special findings were made in other organs.

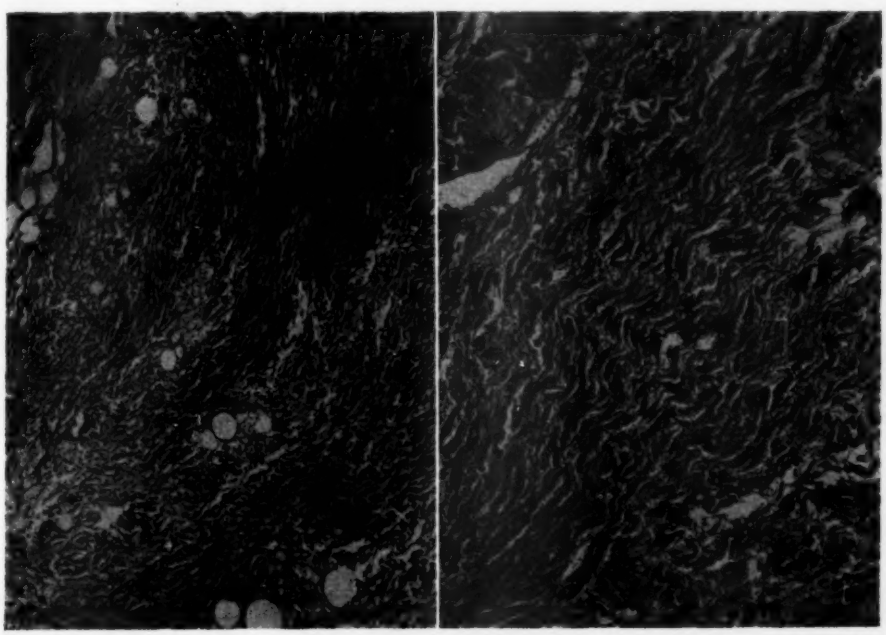

Fig. 2. Fig. 3.

Fig. 2.—An area of the tumor in the subepicardial tissue showing closely packed elongated cells. These are arranged in fasciculated bundles with the nuclei frequently aligned in parallel rows. A modification of Mallory's connective tissue stain. (×85; reduced ¼.)

Fig. 3.—Another area showing the elongated cells regimented in wavy bundles. Note the resemblance of this tumor structure to the peripheral nerve at the upper left margin. Mallory modification. (×155; reduced ¼.)

Histologic examination: Specimens were prepared from different parts of the tumor growth and metastases. Staining of the sections was made by van Gieson's, hematoxylin-eosin, toluidine blue, Mallory's phosphotungstic acid and modified connective tissue stains, and Foot's silver ammonium carbonate methods.

The tumor tissue consisted of small cells with hyperchromatic nuclei, which in the manner of schwannomas formed two different types of tissue, i.e., fasciculated and reticular.

In the former type the cells were elongated, rodlike and closely packed. Both the nuclei and the long, granular cytoplasm fibers which formed polar extensions from the nuclear ends were arranged in wavy bundles, simulating the structure of peripheral nerves (Figs. 2-5). The cells in the reticular tissue were stellate, and their fine cytoplasm fibers formed a syncytial network (Fig. 6). Palisade zones and microcystic formations typical of schwannomas were seen. Stroma-like bundles of collagen were present in small numbers in the closely packed tissue but in larger fibrotic or hyalinized bands in the areas of looser tissue, where necroses, hemorrhages, vascularization and tumor thrombi frequently governed the histologic picture. The replacement of the typical manner of growth was frequently associated also with a notable degree of atypia and polymorphism (Fig. 7). The tissue of the metastases contained numerous cells and was immature. The cells were round and had a dense, hyperchromatic nucleus. No metachromatically staining substances, myofibrils, or giant cells were observed.

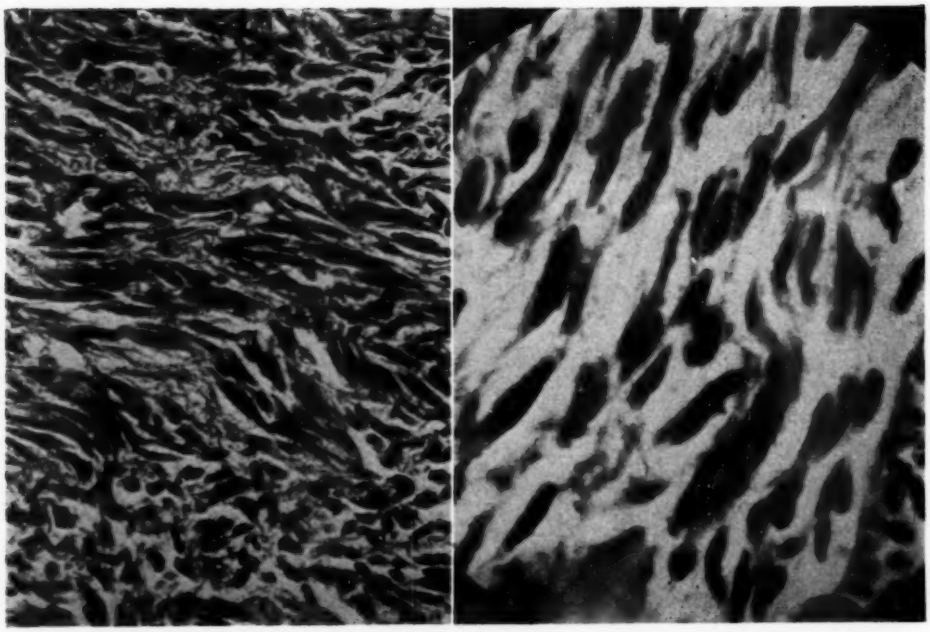

Fig. 4. Fig. 5.

Figs. 4 and 5.—Higher magnifications of the cells in the fasciculated tumor areas. The elongated cells show hyperchromatic nuclei and polar extensions of the cytoplasm. Mallory modification. (×340 and ×750; reduced ¼.)

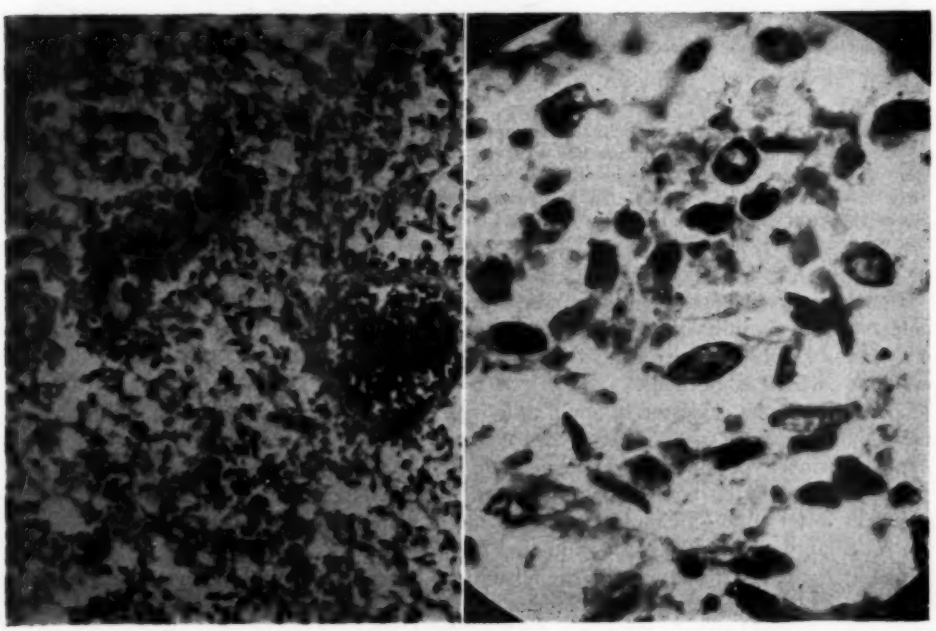

Fig. 6. Fig. 7.

Fig. 6.—A loose and richly vasculated area in the neighborhood of the tumor area in Fig. 2. The cells are small, stellate, and syncytial, the ground substance clear. Mallory modification. (×155; reduced ¼.)

Fig. 7.—Cytologic pleomorphism in a loose atypical tumor area. Mallory modification. (×750; reduced ¼.)

The infiltrative and destructive properties of the tumor tissue were remarkable. Thus the entire muscular wall of the right ventricle was destroyed and partly replaced by hemorrhagic and degenerative tumor tissue. The fasciculated structure of the conus pulmonalis was the result of transversely arranged typical cords of neoplastic cells in this area. In the tumor mass there was also a large number of nerves, which mostly were unmyelinated.

DISCUSSION

A clinically diagnosed case of sarcoma of the heart is described here. According to the literature available to us, only five cases of this disease have previously been diagnosed during life (Popp,[11] Barnes and associates,[12] Shelburne,[13] Weir and Jones,[14] Ravid and Sachs)[15]. In the case now described there was a malignant tumor involving the heart, pericardum, and mediastinum. Histologically it is to be regarded as a malignant schwannoma. Fasciculated Antoni's "type A" as well as reticular "type B" were clearly represented in this neoplasm. In contrast to the case of Kienböck and Redlich mentioned here, the main axis of this tumor mass proceeded anteriorly in a straight sagittal direction, and the mediastinal extension was definitely less and more benign. Clinically and pathologically this case undoubtedly belongs to cardiac sarcomas. The occurrence of this neurogenic sarcoma in the cardiac site is topographically fully in conformity with the anatomic conditions. The cardiac nerve plexus arising in the vagus nerve sends out branches both to the conus pulmonalis and to the interauricular septum. Histologically, the cells in the most differentiated areas of the tumor were typical Schwann cells. Developmentally they are neuroectodermal cells but when mature they greatly simulate fibrocytes, which under normal conditions constitute their natural environment. In tumors arising from peripheral nerves the differentiation naturally is more irregular and more limited to one type, than in the normal nerve, but the similarity of the cell types also in these cases has tended to bring about confusion and disputes concerning the histogenetic group—neuroectodermal or mesenchymal—in which the dominating cells should be included in each case. The deviation of opinions on this point has naturally caused considerable diversity and confusion in the nomenclature. Many writers have set aside the dispute by speaking of a neurogenic type only. We, for our part, are of the opinion that Schwann cells differ from fibrocytes in their formal genesis as well as in special adult features and that a histogenetic differential diagnosis between these tumor cells is possible in at least most cases. On the basis of this explanation, the verified diagnosis of the tumor now described by us is a malignant schwannoma and not a fibrosarcoma.*

Since the mediastinal and pulmonary extension of the tumor in our case might also point a priori to a pulmonary origin, so-called oat-cell bronchogenic carcinomas, in particular, should be excluded in the differential diagnosis. For this purpose we examined a series of small-celled malignant tumors of the lung and observed that they do not show similar differentiation and variation of type as the cardiac sarcoma described by us; however, the difference between the latter and certain types with elongated cells was not very great. This bears out the opinion that the present group of bronchial cancers probably is still heterogeneous and may also include neurogenic tumors.

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*The same conclusion was reached also by Dr. F. Wahlgren, and Dr. G. Lundmark, of Södersjukhuf Stockholm, Sweden, to whom we extend grateful thanks for performing a control examination of our specimens.

In the case described by us, the tumor tissue had also a considerable tendency to regional vascularization, pleomorphism, and atypia. Had not a typical arrangement of the tumor tissue been found, the only possibility remaining would have been to classify the tumor as, for instance, a round-cell, spindle-cell or pleomorphic sarcoma. In fact, the writers consider it possible that some proportion of the undifferentiated sarcomas of the heart reported in the literature may be neurogenic. This circumstance might afford some explanation as to why sarcomas of the heart are chiefly situated in the right cardiac half.

SUMMARY

The authors have described a clinically diagnosed sarcoma of the heart in a 52-year-old man. The sarcoma had invaded the heart, pericardium, and mediastinum. Histologically the tumor was a malignant schwannoma having its origin in the vagus nerve or in the cardiac plexus arising from this nerve.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un homine de 52 annos de etate suffrente de un sarcoma cardiac que esseva diagnosticate durante le vita del patiente. Un revista del litteratura disponibile al autores ha revelate solmente cinque previe reportos de comparabile casos. Le sarcoma habeva invadite le corde, le pericardio, e le mediastino. Histologicamente illo esseva un maligne schwannoma. Su origine esseva in le nervo vage o in le plexo cardiac que depende del nervo vage. Es justificate le identification del sarcoma como un maligne schwannoma e non como un fibrosarcoma.

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Book Reviews

ENDOTHELIUM: ITS DEVELOPMENT, MORPHOLOGY, FUNCTION AND PATHOLOGY. By Rudolf Atlschul. New York, 1954, The Macmillan Company, 157 pages, 9 figures.

The scattered literature concerning vascular endothelium has been collected into a small book that will be of considerable value to those who have a fundamental interest in the endothelium and its problems. It is a subject that is as difficult to study as it is complex in its application. Consequently, the literature is contradictory, controversial, and speculative to a degree that is almost unseemly. In these circumstances, Dr. Altschul has presented a compilation rather than a critical review of our knowledge of the development, structure, function, pathology, and nature of endothelium. While it may be regretted that the author was not more critical, it must be admitted that the subject is so uncertain that a critical approach may be neither feasible nor useful. The reticuloendothelial system has been considered only in relation to endothelium.

The monograph will serve as a valuable and stimulating source book for investigators of all kinds whose problems are intimately bound up with those of endothelium. It is not recommended to the general medical or biological reader.

G. C. M.

HERZKRANKHEITEN IM SÄUGLINGSALTER. By Dr. Ettore Rossi. Stuttgart, 1954, Georg Thieme, 373 pages, 198 figures.

Few fields of medicine have progressed as rapidly in recent years as that of heart disease in infancy, and there is an obvious need for an up-to-date systematic treatise on this subject. Dr. Rossi's book is an admirable answer to this need, save for the fact that the language barrier will limit its usefulness to the small number of American pediatricians and cardiologists who read German. Those whose German is shaky may be glad to know that Rossi's book is written in simple language and is so clearly organized and well illustrated that even an elementary knowledge of the language will suffice.

An introductory chapter gives a condensed summary of the normal range of cardiovascular functions in infants. Of particular interest are electrocardiographic standards from the first hour after birth up to one year. In the largest chapter, congenital malformations are systematically and competently discussed, with a detailed analytical breakdown into approximately forty different types of pathology. The results of the recent developments in heart catheterization, phonocardiography, conventional electrocardiography and vectorcardiography are incorporated. Perhaps the most interesting chapter is that on idiopathic cardiac hypertrophy, which is, according to the author's large clinical experience, quite frequent in infancy and, therefore, was the main object of his own work. The role of various types of infectious myocarditis in the production of hypertrophy is discussed in the first part of this chapter, followed by a detailed description of chronic myocardial degeneration due to disturbance of the carbohydrate and fat metabolism, to electrolyte imbalance, and to other types of disorders. It appears that the term "idiopathic" can often be replaced by more specific clinical entities on the basis of the recent diagnostic development. The relatively short chapter IV discusses cardiac enlargement in extracardial pathology (endocrine disorders, anemia, avitaminosis, etc.), and the last chapter discusses the treatment of cardiovascular insufficiency.

Essentially, the book is aimed at differential diagnosis, and not treatment. Heart surgery is only briefly mentioned, but indications and contraindications for surgery are given. The up-to-date list of references exceeds 1,200, and the book is profusely illustrated with excellent figures, charts, tables, and colored diagrams.

E. S.

Announcements

THE NORTH AMERICAN CHAPTER OF THE INTERNATIONAL SOCIETY OF ANGIOLOGY will hold its Third Scientific Meeting on June 4, 1955, at the Chalfonte-Haddon Hall, Atlantic City, N. J. The scientific program includes eighteen communications and a panel discussion on THE PRESENT STATUS OF VASCULAR GRAFTS IN THE MANAGEMENT OF ARTERIAL DISEASES. Further information may be obtained from Dr. Henry Haimovici, Secretary, 105 East 90th St., New York 28, N. Y.

The II EUROPEAN CONGRESS OF CARDIOLOGY will be held in Stockholm, Sweden, September 10 to 14, 1956. Information regarding the Congress may be obtained from the General Secretary: Dr. Karl Erik Grewin, Söderjukhuset, Stockholm S, Sweden.

The 28th Annual Scientific Session of the AMERICAN HEART ASSOCIATION will be held on Oct. 22, 23, and 24, 1955, at the Jung Hotel, New Orleans, Louisiana. Meetings sponsored by the Council on Community Service and Education and the Council on Rheumatic Fever and Congenital Heart Disease will be held on October 23 and 24. The Assembly Panels will follow the Scientific Sessions on October 25, and the General Assembly will be held on the morning of October 26.

Other important events during the meeting include the annual dinner of the American Heart Association on the evening of October 24 and the Assembly luncheon at noon on October 25.

All those wishing to present papers must submit abstracts for review by the Program Committee. Abstracts shall not be more than 300 words and must be submitted in duplicate before July 1, 1955, to the Medical Director, American Heart Association, 44 East 23rd Street, New York 10, New York. Abstracts should contain in summary form the results obtained and conclusions reached.